

How to Cite:

Singh, P. K., & Easwari, T. S. (2022). Fabrication of floating tablets using bark extract of *azadirachta indica* for the treatment of peptic ulcer. *International Journal of Health Sciences*, 6(S9), 1554–1570. <https://doi.org/10.53730/ijhs.v6nS9.12614>

Fabrication of floating tablets using bark extract of *azadirachta indica* for the treatment of peptic ulcer

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Abstract--Targeted release of drugs in the upper intestines can be achieved by using floating drug delivery systems (FDDS). *A. indica* has been the most commonly used traditional medicine for the treatment of peptic ulcers in rural India. This study's *A. indica* bark extract floating tablets are designed to keep drug in the stomach longer, boost its bioavailability, and target the ulcer in the stomach. Hydrocolloids (such as HPMC and carbopol 934P) were employed to expand an FDDS, as were sodium bicarbonate (NaCl) and citric acid. They were examined for their pre-compression properties, physical qualities, buoyancy, lag time, in vitro release, and swelling index before compression. It was determined which formulations worked best for the various HPMC viscosity grades, carbopol 934P concentrations and mixtures. Experiment results showed that F2 was able to maintain drug release (95 percent) for 12 hours and remained buoyant at the same time. The improved formulation (F2) did not alter buoyancy time, drug content, and in vitro dissolution after three months at 40°C/75 percent RH. Tablets are cost-effective and may solve absorption issues. *A. indica* bark extract significantly reduced ulcer index and percentage of ulcer formation in animals. It also restored secretions of gastric fluid and antioxidant levels in the animals.

Keywords--- *Neem*, peptic ulcer, floating tablet, gastrin, pepsin.

Introduction

Inflammation and necrosis of the mucosa or submucosa result in a peptic ulcer (PU), which can be caused by various pathogenic factors. It is most common in the mucosa of the gastrointestinal tract, particularly the stomach and duodenum, which secrete gastric acid. As many as 5 percent to 10 percent of people in the general population have a lifetime prevalence of PU of 0.1 percent to 0.3 percent (Zhao et al., 2022). As a result, early detection and prevention of PU are critical to reducing the health care costs of the global population. Peptic ulcer disease (PUD) includes ulcers in the esophageal, duodenal, and gastric lining. Epigastric pain is the most common symptom of PUD. Patients who are infected with *H. pylori* are typically treated by removing the bacterium from their digestive tract. Proton Pump Inhibitor, Amoxicillin, and Clarithromycin are among the most commonly prescribed first-line treatments for patients with bacterial vaginosis, but there are a number of other combinations that can also be used (Chan et al., 2015; Avitt et al., 2019). Surendra and Rafat (2016) PUD has long been treated with a wide variety of herbal remedies all over the world. PUD can be treated with 279 plants from 89 families identified in an assessment by Ardalani and his colleagues. Because of the relative safety, availability, and lower cost of herbal remedies compared to the vast majority of conventional medications, they have the potential to be used to treat conditions like PUD (Ardalani et al., 2020). Some herbal materials have been subjected to toxicological studies, the findings of which have contributed to a greater level of trust in herbal products (Adi-Dako et al., 2018). *Azadirachta indica*, the tree for which the common name "neem" refers, is indigenous to India. Ayurvedic, Chinese, homoeopathic, and unani medicines all use this plant as a traditional medicine (Alzohairy, 2016; Eid et al., 2017) in Asia and Africa. To reduce as well as cap/stabilize, the bark extract contains a variety of phytochemicals (Saini et al., 2022). It is common practise in India to use *A. indica*'s young leaves and flowers as a vegetable and a traditional medicine for a wide range of ailments, including headaches and insomnia (Subapriya R, Nagini, 2005; Govindachari et al., 2005). To name just a few of the compounds found within the *Azadirachta indica* leaf's constituents: Nimbin, Nimbolidene, and Nimbananene (Ali, 1993; Hossain et al., 2011; Gokhale et al., 2013; Bandyopadhyay et al., 2004). Because of their low bioavailability and short retention time at the target site, herbal medicines have a reduced therapeutic effect. Bilayer floating tablet (FDDS) is the primary method for extending gastric residence times in the stomach, and it plays a key role in this approach. Peptic ulcers, gastritis, Zollinger-Ellison syndrome, indigestion, and other gastrointestinal tract infections are among the conditions for which it is best suited, though it can also be used systemically. Acid-labile drugs with short half-lives are well-served by FDDS. It also increases the residence time of drugs, decreases drug waste, and improves bioavailability (Namdev and Jain, 2019). The development of FDDS is currently being aided by a wide range of technologies. Bilayer floating tablets, which incorporate novel drug delivery systems, have also expanded the role of FDDS. For FDDS, polymers are critical because they act as carriers for the drug and regulate its absorption in the stomach as well as its protection from the gastrointestinal tract. FDDS is also a simple, inexpensive, and more convenient method for delivering drugs in a dual mode (Sahu et al., 2021). As a result, the current investigation aimed to formulate *A. indica* bark extract floating tablets and determine its antiulcer activity against peptic ulcer in experimental model.

Materials and Methods

A. Drug and Chemicals

Nimbin, indomethacin, ranitidine, chitosan, sodium bicarbonate, magnesium stearate, citric acid, talc, and HPMC K 100M were procured from Sigma Aldrich, USA. Distilled water was used throughout the study.

B. Collection and extraction of *A. indica* bark extract

The botanical garden of the institute provided the source of this *A. indica* stem. The head of the botany department confirmed its authenticity. The herbarium of the institute deposited a specimen (voucher number 0243) as a record of the transaction. Peeling and chopping *A. indica* bark required a sharp knife. Drying and grinding ash generated powdered ash. 20 mg of each sample was extracted for 6 hours in 250 millilitres of methanol, and the residues were kept at 4°C until dried under reduced pressure in a rotatory evaporator (Khadri et al., 2010).

C. Analytical Method Development

To estimate the extract's drug release, an accurate and reproducible method must be developed. As a result, the UV Spectroscopic method was used to estimate the extract.

D. λ Max Determination by UV Spectrum

To make 1000 mcg/ml stock solutions, 100 mg of dry extract of the drug was dissolved in 100 ml of solvent. In addition, the UV spectroscopic method was used to analyse the 10 mcg/ml solution, scanning it from 200 to 400 nm in wavelength.

E. UV Spectroscopic Calibration of Drug Extract

Prepare a stock solution of 1000 mcg/ml by accurately weighing the amount that was dissolved in the solvent. To determine the absorbance at 207 nm, further dilutions were made in the range of 0, 25, 50, 100, 200, 300, and 400 micrograms per litre solutions. Microsoft Excel was used to create the calibration curve. Blank was used to determine the absorbance of various solutions. The absorbance was then plotted against the concentration, and regression analysis was then performed.

F. Estimation Of Active in The Extract by HPLC

❖ Standard preparation

The 3.0 mg reference standard should be weighed precisely, transferred to an endpendroff tube, and made into a stock solution using appropriate diluents. The stock solution should then be used to prepare linearity solutions at concentrations of 10, 20, 30, 40, and 50 ppm, using the same diluents.

❖ Sample preparation

Precisely weigh 5 gm of herbal extract into a 100 ml volumetric flask and dilute to the desired volume with appropriate diluents.

❖ Diluents

0.5 % Acetic acid: Methanol (45:55 v/v)

❖ Chromatographic parameter

Column : Kromasil C18 (250 x 4.6 mm) 5 μ

Mobile phase : 0.5 % Acetic acid: Methanol (45:55 v/v)

Retention time : About 16 min
 Run time : 25 min
 Wavelength : 254 nm
 Column Temperature: 25°C
 Injection Volume : 20 µl

G. Drug-Polymer Interaction Study

Through the use of Fourier transform infrared spectroscopy (FTIR), the interaction between drugs and polymers was investigated. Neem bark extract, polymers, and an API polymer combination were all used to collect the spectra for these analyses. FTIR spectroscopy was used to investigate the drug-polymer interactions. For Neem bark extract physical mixture of polymers and physical mixture of medicine with polymers, FTIR – spectrophotometer was used to capture spectra (FTIR 8400S; SHIMADZU, Japan). The scanning range was 400-4000cm⁻¹ and the resolution was 1 cm⁻¹ (Devi VK, Jain N, Valli KS et al 2010).

H. Formulation Studies

All of the tablets in this study were prepared using the effervescent method. HPMC K100M polymer and other ingredients such as magnesium stearate, talc, citric acid, and sodium bicarbonate are used in the tablet manufacturing process. Since HPMC K 100M is a matrix forming and low density polymer, it is a suitable polymer for a floating drug delivery system (Lakshmaiah et al., 2014). All of the ingredients were weighed using an electronic balance after passing through sieve number 80. To make a uniform tablet, we used a mortar and pestle to combine the extract with HPMC K100M, sodium bicarbonate, and carbopol 934P. Talc and magnesium stearate were added at the end to complete the mix. Trial and error were used to determine the concentrations of the three polymers that were ultimately chosen. Based on previous research, sodium bicarbonate and citric acid were used as gas-generating agents in the ratio of 1.0: 1.0. (Salve, 2011). PVPK30 was used as a binding agent. A combination of talc and magnesium stearate was used to lubricate the powder and improve its flow. To create tablets, the tablet mixture was weighed out individually using a single punch tableting machine and compressed (Cadmach, Ahmedabad). Table 1 lists the formulas for each of the six different formulations (F1–F6).

Table 1: Formulation of A. indica bark extract floating tablets

S. No	Ingredients	F ₁	F ₂	F ₃	F ₄	F ₅	F ₆
1	A. indica bark extract powder	240	240	240	240	240	240
2	Chitosan	200	--	--	---	100	100
3	HPMC K100M	--	200	--	100	--	100
4	Carbopol 974 P	--	--	200	100	100	---
5	Sodium bicarbonate	20	20	20	20	20	20

6	Citric Acid	20	20	20	20	20	20
7	PVPK30	10	10	10	10	10	10
8	Magnesium Stearate	5	5	5	5	5	5
9	Talc	5	5	5	5	5	5

❖ Evaluation of floating tablets

Diameter and thickness were measured with Vernier callipers. Monsanto hardness tester was used to assess tablet hardness. A Roche friabilitor measured brittleness. Using the individual tablet weights, 20 tablets from each formulation were averaged.

❖ Buoyancy time

When a dosage form floats to the surface, it's called the floating lag time (FLT) or buoyancy lag time (BLT). The USP type II (paddle) apparatus, which resembles an animal's body, was used to test 900 mL of 0.1N HCl solution at 37°C.

❖ In vitro dissolution studies

In vitro dissolving investigations employed USP type I (basket). Dissolution media was 900 mL 0.1N HCl. Using a thermostat, 37±0.5°C was set for the dissolving bath. Tablet was placed in basket. Motor speed was 100 RPM. When a sample was removed, 5 mL of dissolving medium was added to maintain volume. 30 mL chloroform extracted aliquots were analysed spectrophotometrically at 251 nm against blank chloroform for drug release. Three trials were run. Researchers graphed cumulative release versus time (in hours).

❖ Analysis of release kinetics

The release mechanism was identified when the release data were fitted to various kinetic equations, such as Higuchi and Korsmeyer-Peppas, and R² values were determined for the release profile corresponding to each model. This allowed for the discovery of the release mechanism. It can be seen in Table 2, the findings are quite interesting.

Table 2: Release kinetics of floating tablet

Formulation	Zero order R ²	First order R ²	Higuchi R ²	Korsmeyer R ²
F1	0.9574	0.9194	0.9862	0.9886
F2	0.9638	0.9147	0.9882	0.9803
F3	0.9483	0.8947	0.9104	0.9964
F4	0.9538	0.9482	0.9914	0.9966
F5	0.9709	0.9221	0.9880	0.9935
F6	0.9943	0.9377	0.9693	0.9951

❖ **Experimental Animal**

In the experiment, both male and female albino rats weighing between 150 and 170 g were employed. The study was approved for further pursuit by the Institutional Animal Ethical Committee. The animals were given one full week to acclimate themselves to their new environment before the beginning of the trial. A temperature of 25 degrees Celsius and a relative humidity of 65.2 percent were kept constant during the light-dark cycle that lasted for 12 hours.

❖ **Experimental protocol**

Randomization was performed on five groups, each consisting of seven albino rats. The animals in Group 1 received nothing but water that had been distilled (the normal control). Doses of indomethacin alone were given to the rats that made up group 2 of the study (as a negative control). The typical treatment for Group 3 was ranitidine, at a dose of 20 mg/kg of body weight. The animals in Group 4 were given a floating tablet of an extract of *A. indica* bark containing 20 mg/kg body weight (F2). Prior to the administration of indomethacin, the reference medication (Ranitidine) and Formulation (F2) were both given to the subjects for a period of 21 days. Throughout the duration of the experiment, these were administered via oral administration once per day utilising an oral incubator. Ad libitum access to both food and water was provided.

❖ **Isolation of stomach and collection of gastric juice**

On the twenty-third day, the animals were humanely killed by cervical dislocation (4 hours after ulcer induction). After the abdomen had been opened up, the stomach was then extracted and removed. After opening the stomach along its greater curvature, the contents of the stomach were removed and placed into a tube that was placed in a centrifuge. After centrifuging at 3000 rpm for ten minutes, five millilitres of distilled water were added to the mixture. Following that, the supernatant that had been collected was utilised in a variety of different types of biochemical investigations. The stomachs were kept in 0.1 M phosphate saline buffer (1:4 (w/v), pH 7.4), which allowed for microscopic observation as well as homogenization before the process.

❖ **Determination of gastric secretion parameters**

Toepfer's indicator were utilised in order to determine the volume of stomach acid secretion in the supernatant (2 ml). We measured the pH of the gastric juice with a pH metre. To determine the specific pepsin activity and mucin concentration, we followed the protocols established by Sanyal et al. and Cornell et al.

❖ **Quantification of ulceration**

The method that was utilised to measure the degree of ulceration after indomethacin was given to animals was the one that was outlined by Szabo and Hollander. We graded the severity of vascular congestion and lesions/hemorrhagic erosions on a scale from zero to five using a dissecting microscope fitted with a square-grid eyepiece, as indicated in Table 1. When calculating the percentage of mucosal damage, the total surface area of the glandular stomach was converted to millimetres squared and utilised as the basis for the calculation. It was determined that the ulcer index, or U.I., was the best way to express the average ulcer score for each animal, and the following expressions were utilised to determine the percent-age of inhibition against ulceration:

U.I. = [Ulcerated area/total stomach area] × 100.

%Ulcer inhibition = [U.I. in control – U.I. in test] × 100/U.I. in control.

❖ **Stomach homogenate and antioxidant indices**

After scoring an ulcer, the entire stomach was ground into powder with liquid nitrogen. Each powdered tissue was homogenised (0.5 g) and centrifuged at 2500 rpm for 10 minutes at 4°C in 0.1 M phosphate saline buffer (1:4, pH 7.4) Frozen supernatants were used for the enzyme assay because they released tissue enzymes entirely. Two studies used stomach homogenate to assess SOD and MDA lipid peroxidation levels (lipid peroxidation activity).

Statistical Analysis

Mean ± SEM (n=7) One-way ANOVA and Student's t-test were employed to discover significant differences (p <0.05) between treatment groups in this investigation.

Result

A. UV Spectroscopy (Determination of λ_{max})

The UV spectra of diluted solutions of various Nimbin concentrations in the mobile phase were recorded using a UV spectrophotometer. At 214 nm, the greatest absorption was found. To detect Nimbin, this wavelength was chosen.

B. Preparation of Standard Curve of Nimbin

An acid buffer pH 1.2 solution of 100 mg of medication dissolved in acid buffer pH 1.2 was produced to 100 ml by adding acid buffer pH 1.2. Diluted to pH 1.2 acid buffer from this solution was 10 ml. For the concentrations of 5-25 µg/ml, we produced serial dilutions of the stock solution. We used a 214 nm absorbance measurement to determine the solution's absorbance value.

C. HPLC study

❖ **System Suitability**

Before examining a sample, chromatographic systems must be suitable. After setting up chromatographic equipment, let HPLC stabilise for 30 minutes. Record chromatograms of at least six replicate LMS standard injections to evaluate system appropriateness characteristics such as tailing factor [NMT 1.5], theoretical plate count [NLT 3000], and percent RSD for peak area of six replicate LMS standard injections [percent RSD NLT 2.0]. Table shows system suitability. Table 3 showing HPLC quantification of nimbin.

Table 3: HPLC quantification of nimbin

Injection of Std.	Retention Time	Area of Nimbin	Average Area	% RSD	No. of Theoretical Plates	% RSD	Tailing Factor
1	2.85	8120699	8157210.83		7649	0.50	1.48
2	2.85	8130297			7674		1.48

3	2.84	8160363		0.32	7624		1.73
4	2.84	8179754			7692		1.73
5	2.84	8169642			7663		1.69
6	2.84	8182510			7736		1.53

D. Post-compression evaluation

❖ Weight Variation

At the beginning of several trials, weight variation was noted, but in the final trial tablet, the weight variation was found to range between 500 ± 1.24 and 500 ± 4.61 mg (Target weight – 500 mg/Tablet), indicating that it is within standard official limits.

❖ Thickness Evaluation

When determining the thickness of the tablets, a Vernier Caliper was utilised. There is no noticeable difference in the thickness of the tablet between the two different strengths.

❖ Hardness Test

With the help of a Monsanto hardness tester, we were able to determine the tablet's hardness in kilogram per square metre. Within a range of 5.2 ± 0.27 kg/cm² to 7.0 ± 0.51 kg/cm², tablets' hardness was determined to be consistent.

❖ Friability Test

Roche Friabilator was used to test the material's capacity to break down into friable pieces. Tablet friability ranged from 55.25% to 0.89% for a sample of 20 tablets tested. This means the manufactured pills are mechanically stable because they are fewer than the standard limit of 1 per cent.

❖ Evaluation of formulated tablets

All formulas had a diameter between 11.04 and 11.86 millimetres and a thickness between 3.21 and 3.43 millimetres. 5.2 to 7.0 kg/cm² of hardness were measured. The USP standards for friability and weight homogeneity were met by all formulations (Table 4).

❖ Drug content uniformity

F1 to F6 included 97.4 ± 1.54 percent to 99.91 ± 1.98 percent of Nimbin, according to the results. The findings are summarised in the following table.

❖ Tablet density

The density of the tablets ranging from 0.82 g/cc to 0.99 g/cc. For floating of tablets the density of tablets should be less than the gastric fluid density (1.004). So it gives the successive result.

❖ Buoyancy lag time studies

The floatability of all tablet formulations was good and lasted for roughly 10 hours. Table shows how the floating lag time varies among all formulations. It was found that Formulation F2 had the lowest latency time, whereas F3 had the highest latency time. Table 3 displays the buoyancy time for various formulations. FLT of all formulations was determined to be less than 5 minutes. Swollen polymer gellifies sodium bicarbonate produced by carbon dioxide in acidic solution (hydrocolloids). So, the dose form floats. FLT can be explained by the time needed for dissolving media to infiltrate tablet matrix and develop swelling layer for CO₂ trapping. Tablet mass drops as CO₂ and medicine are released from the matrix. As the solvent front entered HPMC K100 M's glassy polymer layer,

tablet volume increased. Reduced tablet density extends flotation time past 8 hours. The latest study enhanced floating pills' 8-hour stability and 99 percent drug release. The chemicals utilised in formulation development were chosen to ensure that the medicine would be released for 12 hours. Polymers' swelling and density, as well as a gas-generating agent, all play a role in floating medicine delivery (Arora et al., 2005). Carbon dioxide is formed when sodium bicarbonate combines with stomach juices and creates gas. An inflated matrix holds the gas in place and gives the formulation buoyancy (Arora et al., 2005). HPMC K100M was utilised because of its high viscosity and swelling properties.

Table 4: Evaluation of *A. indica* bark extract floating tablets

Formulation	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm ²)	Friability (%)	Diameter (mm)	Drug contents (%)	Buoyancy (min)	Density (g/cc)
F1	500 ± 1.24	3.25 ± 0.12	6.3 ± 0.19	0.79	11.04 ± 0.31	99.52 ± 2.51	2.51 ± 1.35	0.97
F2	500 ± 2.17	3.43 ± 0.46	5.2 ± 0.27	0.89	11.13 ± 0.21	98.69 ± 1.62	1.80 ± 1.12	0.89
F3	500 ± 1.61	3.21 ± 0.23	7.0 ± 0.51	0.85	11.33 ± 0.26	99.91 ± 1.48	3.91 ± 1.56	0.93
F4	500 ± 1.45	3.37 ± 0.25	6.1 ± 0.37	0.52	11.40 ± 0.32	99.48 ± 2.73	2.31 ± 2.74	0.99
F5	450 ± 2.36	3.28 ± 0.59	6.5 ± 0.65	0.67	11.86 ± 0.48	97.40 ± 1.54	2.70 ± 1.98	0.82
F6	450 ± 1.52	3.41 ± 0.36	5.5 ± 0.24	0.71	11.52 ± 0.24	99.94 ± 1.98	2.00 ± 1.31	0.94

❖ Swelling Study of Tablets

Results show that formulation containing HPMC K100M in higher concentration had higher % swelling than formulations containing Carbapol and Chitosan. Formulation F2 had the maximum swelling of 144.25 after 12 hours and formulation F3 had the lower swelling capacity of 133.83 after 12 hours (Table 5).

Table 5: Percentage swelling of formulation F1 – F6

Time (hr)	Formulations					
	F ₁	F ₂	F ₃	F ₄	F ₅	F ₆
1	79.28 ± 25	115.37 ± 1.5	73.66 ± 1.34	85.36 ± 1.85	95.28 ± 1.91	92.81 ± 1.2
2	95.42 ± 1.2	124.42 ± 1.4	92.57 ± 1.2	99.35 ± 1.4	105.32 ± 1.5	102.38 ± 1.8
3	103.59 ± 1.4	130.43 ± 1.34	99.72 ± 1.5	105.25 ± 1.91	112.54 ± 1.28	108.36 ± 1.41

4	106.72 ± 0.85	134.73 ± 2.10	104.69 ± 1.8	111.52 ± 1.20	120.31 ± 1.8	114.31 ± 4.25
5	112.48 ± 1.3	139.23 ± 1.2	110.39 ± 1.28	116.21 ± 1.25	126.63 ± 1.21	121.56 ± 1.4
6	117.39 ± 2.1	141.1 ± 1.57	115.19 ± 1.5	119.28 ± 1.4	131.54 ± 1.5	127.56 ± 3.89
8	123.24 ± 1.25	142.36 ± 1.83	121.91 ± 1.85	126.36 ± 1.2	137.87 ± 1.2	133.39 ± 1.5
10	128.69 ± 1.8	142.89 ± 1.59	125.73 ± 2.25	131.8 ± 1.47	139.26 ± 1.2	137.52 ± 1.19
12	134.74 ± 1.4	144.25 ± 1.20	133.83 ± 1.2	137.38 ± 1.5	140.17 ± 1.25	139.61 ± 1.85

❖ In vitro drug release studies

The dissolution medium used to test the release of the tablet formulations was 0.1N HCl for in vitro drug release. Floating tablet batches F1 through F6 were tested for in vitro A. indica release, and the results are shown in Table 1. Using the dissolution profiles, one can compare the release profile of a medicine with varied polymer concentrations from batches. An A. indica bark extract's gelling capabilities may have been responsible for the drug's long-lasting effects. Figure 2 shows the in vitro release of HPMC K100M at various doses. The drug release rose from 82.13 ± 1.25 percent to 95.58 ± 1.20 percent when HPMC K100M concentration was increased from 100 (F5) to 200 mg (F2), respectively. Gases are created in these systems by using sodium bicarbonate. After coming into touch with stomach acid, it produces gas. It is trapped in the water-soluble polymer matrix, which floats in the stomach's acidic environment. Tablet 6 release is slowed because sodium bicarbonate, which is alkaline, creates an alkaline microenvironment.

Table 6: In vitro dissolution result for formulation of floating Tablets

Time (hr)	Formulations					
	F ₁	F ₂	F ₃	F ₄	F ₅	F ₆
1	7.9±.25	5.81±1.5	6.72±1.34	5.48±.85	4.29±1.91	3.02±1.2
2	24.58±1.2	19.18±1.4	11.13±1.2	16.16±1.4	14.53±1.5	16.24±1.8
3	42.2±1.4	33.21±1.34	19.92±1.5	30.48±1.91	27.83±1.28	28.72±1.41
4	53.48±.85	45.63±2.10	28.63±1.8	38.21±1.20	35.51±1.8	35.92±.25
5	62.32±1.3	58.66±1.2	40.61±1.28	47.39±.25	44.79±1.21	47.27±1.4
6	71.05±2.1	67.73±1.57	51.57±1.5	59.98±1.4	56.58±1.5	52.64±.89
8	80.91±.25	80.27±1.83	63.18±.85	72.53±1.2	63.53±1.2	65.58±1.5
10	85.11±1.8	90.31±1.59	74.47±.25	80.11±1.47	75.43±1.2	80.32±1.19
12	87.23±1.4	95.58±1.20	80.21±1.2	85.76±1.5	82.13±1.25	90.47±.85

❖ Optimization of tablet formulation

Drug release formulations were fine-tuned based on parameters such buoyancy time and percent cumulative release percent. All formulations had buoyancy times between 3.5 and 5 minutes. The range of the cumulative drug release percentage was between 80.21 and 95.58. F2 was found to be the best formulation. There was a 95.58 percent cumulative drug release and a buoyancy time of 1.80 mins.

❖ Analysis of release kinetics

In order to better understand the release rate kinetics and mechanism of the drug from tablet formulations, it was required to employ mathematical equations such as those from the first-order kinetics equation, zero-order kinetics equation, and the like. Table 4 summarizes the findings of the study. When data were treated with Higuchi's equation to learn about the mechanism of drug release, a poor fit was obtained. The poor correlation coefficient values indicated that no formulation followed the first-order kinetics of the experiment. The best fits for the zero-order and Korsmeyer and Peppas' equations were $R^2 = 0.945-0.9912$ and $0.9817-0.9982$. Drug release is controlled by Fickian diffusion when n is 0.5, while transport is case II when n is 1.0. (swelling-controlled drug release). To exhibit non-Fickian diffusion, n values of between 0.5 and 1 indicate the anomalous transport. All formulations with n values ranging from 0.6242-0.8408 exhibited an abnormal transport mechanism, in which the drug release mechanism is controlled by diffusion as well as polymer relaxation.

❖ Oral safety of test drug

A. indica bark extract floating tablets were safe at the dose of 2000 mg/kg body weight, no behavioural change was seen in rats. There was no mortality among the animals, and they were all active. Floating pills of *A. indica* bark extract exhibited a fatal dosage of more than 2000 mg/kg BW when taken orally.

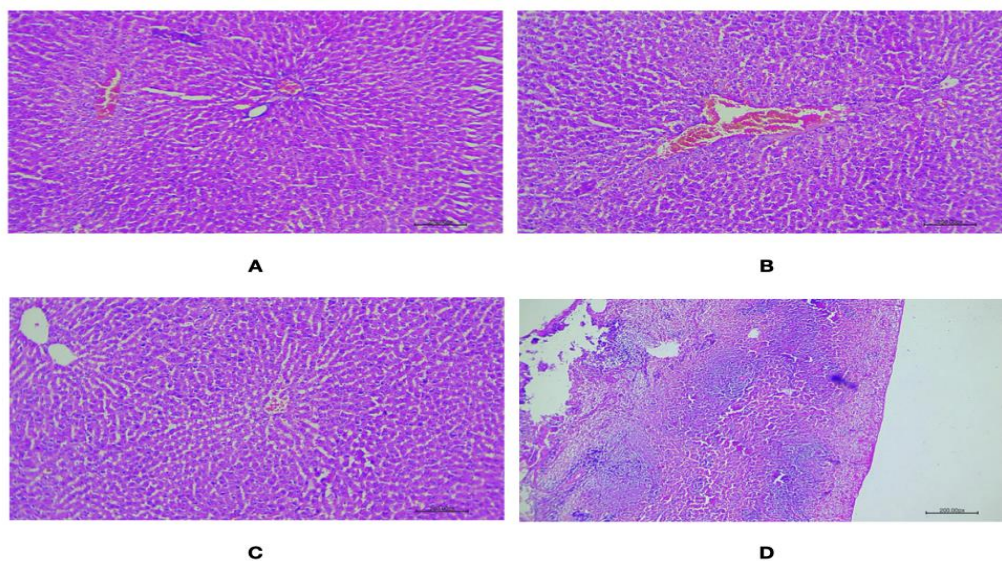
❖ Effect of *A. indica* bark extract floating tablet on Ulcer Index and Percentage Protection

With regular Ranitidine and *A. indica* bark extract floating tablet, ulcer index decreased significantly ($p < 0.05$) from the positive control compared to both groups (Group 2). *A. indica* bark extract floating tablet pre-treated group had a similar percentage of ulcers inhibited compared to the standard group. Table 7 shows the results of the experiment. Figure 1 showing histopathology slides for different treatment groups.

Table 7: Efficacy of *A. indica* bark extract floating tablet against peptic ulcer

Groups	Drug	Ulcer index	Percentage inhibition
Group - 1	Distilled water	0	0
Group - 2	Indomethacin	87.48±2.66	85.71±0.10
Group - 3	Ranitidine	23.06±1.43 *	73.48±1.32
Group - 4	F2	32.28±0.85 *	64.04±1.35

Data are represented as mean \pm SEM (n=7), significantly different at *p value <



0.05 as compared to positive control.

Figure 1: Histopathology of rat stomach after treatment with the test drug

A = Normal control (Distilled water), B = Positive control (Indomethacin), C = Standard group (Ranitidine), D = Test group (F2)

❖ Effect of *A. indica* bark extract floating tablet on gastric secretion parameters

Table 8 shows the effects of floating tablets on gastric secretion parameters. F2 significantly ($p < 0.05$) restored the gastric secretion parameters. Gastric acid secretion was restored to 3.35 ml, pH 4.44, pepsin level restored to 225.85 and mucin level was 151.57 after administration of test drug.

Table 8: Efficacy of *A. indica* bark extract floating tablet on gastrin secretion parameters

Groups	Drug	Gastric acid	pH	Pepsin activity	Mucin activity
Group - 1	Distilled water	2.07 \pm 0.61	6.42 \pm 0.38	183.57 \pm 4.11	171.71 \pm 7.02
Group - 2	Indomethacin	5.61 \pm 1.78	2.72 \pm 0.44	257.85 \pm 6.75	123.14 \pm 5.48
Group - 3	Ranitidine	2.41 \pm 0.78	5.98 \pm 0.24 *	194.71 \pm 7.06 *	168.71 \pm 3.40 *
Group - 4	F2	3.35 \pm 0.81 *	4.44 \pm 0.51 *	225.85 \pm 3.80	151.57 \pm 3.77 *

Data are represented as mean \pm SEM (n=7), significantly different at *p value < 0.05 as compared to positive control.

❖ Effect of *A. indica* bark extract floating tablet on antioxidant Levels

In the positive control group, the MDA level (Figure 2) rise significantly, and the antioxidant levels decreased simultaneously. Pre-treatment with *A. indica* bark extract floating tablet and the standard medicine Ranitidine, on the other hand, considerably ($p < 0.05$) lowered the MDA levels. The SOD and CAT activities in the positive control group were noticeably lower as compared to the normal control group's levels. Pretreatment with a floating tablet containing *A. indica* bark extract significantly increased SOD (Figure 3) and CAT (Figure 4) activity in the positive control group, but to a lesser extent than with the conventional prescription ranitidine.

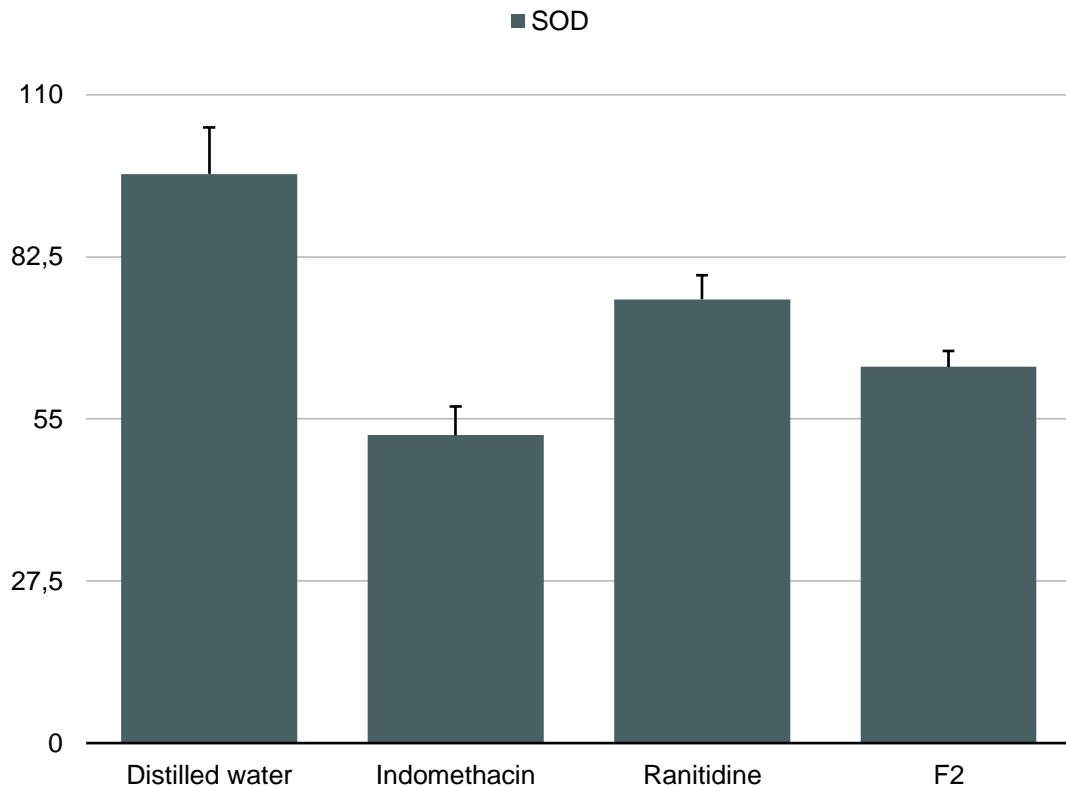


Figure 2: Effect of bark extract on SOD level of rat

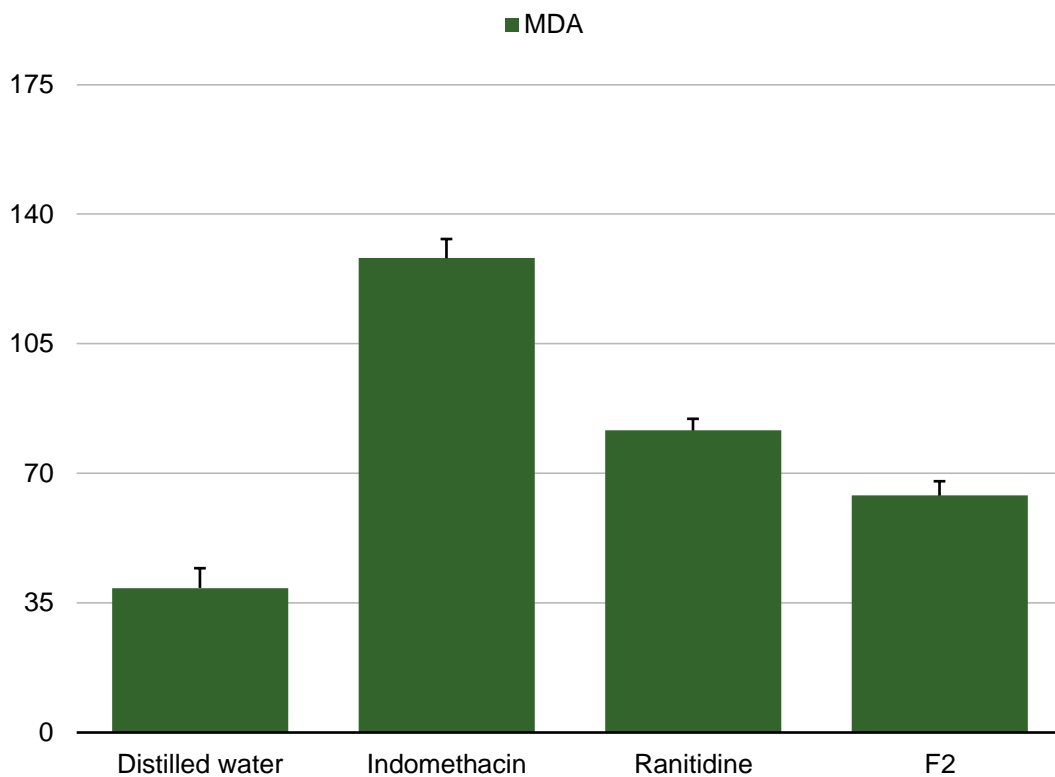


Figure 3: Effect of bark extract on MDA level of rat

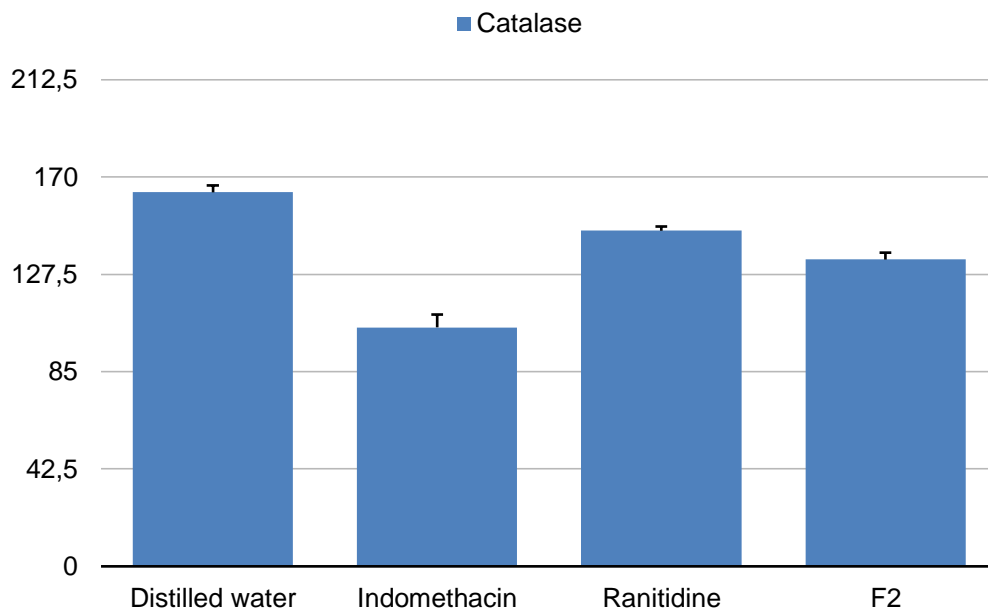


Figure 4: Effect of bark extract on catalase level of rat

Discussion

The word "peptic ulcer" refers to both gastric ulcers and duodenal ulcers, which are both frequent. It's possible that the aggressive and defensive aspects are out of balance. Many efficient antiulcer treatments have long been used in the treatment of peptic ulcers, however these medications are not without side effects. A constant demand for safe anti-ulcer medications exists due to the significant morbidity associated with this condition, prompting researchers to investigate into safer herbal remedies (Rao et al., 2002). The antiulcer and antioxidant properties of *A. indica* bark extract floating tablet were studied in experimental animal models in this work. As a precautionary measure, an acute toxicity study was conducted to determine the safest amount for experimentation. There were obvious stomach lesions and an increase in ulcer index following acute dose of Indomethacin. In the groups pre-treated with *A. indica* bark extract floating tablet, the intensity of stomach lesions and the ulcer index was significantly reduced. Researchers found that a floating tablet containing an *A. indica* bark extract had cytoprotective properties. Gastric acid release is inhibited by parietal cells, which produce mucus as a result of prostaglandins' stimulation of mucus production. Because Indomethacin inhibits prostaglandin formation, it damages gastric and duodenal cells by reducing prostaglandin levels (Wallace and Sharkey, 2011). When MDA levels were increased in the positive control group, enzyme activity decreased in the stomach. As the MDA level rises, and the antioxidant defence mechanism weakens, this indicates peroxidation of lipids (Tandon et al., 2004). Gastric mucosal damage, which is linked to enhanced lipid peroxidation, may be the cause of the large increase in oxygen free radical production. It is necessary for cells to have an abundance of antioxidant enzymes to prevent oxidative damage. SOD and Catalase levels were enhanced after a week of treatment with *A. indica* bark extract floating tablet. MDA levels were reduced by 75%. *A. indica*'s anti-ulcer and stomach-protective properties have been the subject of numerous investigations. The presence of phytoconstituents in *A. indica* bark extract floating tablet may explain its antiulcer and antioxidant properties.

Conclusion

In order to create floating tablets of *A. indica* bark extract, the following ingredients were utilised: chitosan, HPMC K100M, sodium bicarbonate, talc, and magnesium stearate. Tablet size, hardness, uniformity of weight, friability, buoyancy time, and in vitro drug release all fell within acceptable ranges when formulated tablets were evaluated for their physicochemical properties. At a temperature of 37 degrees Celsius, in vitro dissolution tests for the floating tablets were conducted in 0.1N hydrochloric acid. Within the first 12 hours, around 93–96 percent of the medication was released. In comparison to the other created formulations, Formulation F2 exhibited a floating behaviour that was successful, and it also controlled the release of the drug more effectively. The Korsmeyer-Peppas model and zero-order kinetics are the ones that fit the formulated floating tablets the best. The value of n for all of the formulations was found to be in the range of 0.624-0.84, which indicates anomalous transport. This means that the drug release mechanism is controlled by both diffusion and polymer relaxation. It is possible to draw the conclusion that chitosan, sodium bicarbonate, and HPMC

K100M, when used together, have the potential to be useful polymers for gastroretentive drug delivery systems. In order to lengthen the amount of time that an extract spends in the stomach, which in turn increases its bioavailability, floating tablets containing *A. indica* bark extract can be created. According to the findings, there is a promising possibility for using floating tablets containing an aqueous extract of *A. indica* as an alternative to the usual dosage form.

Declaration

The authors declared no conflict of interest.

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