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FORMULATION AND EVALUATION OF POLYHERBAL ANTI ULCER TABLETS

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ABSTRACT
The aim of the present study was to formulate and evaluate polyherbal tablets having floating property to cure ulcer. Oral route of administration of drug is more popular due to its easy administration and more patience compliance. Although in some cases like ulcer conventional tablets are not so effective when a local delivery of drug and a longer gastric retention time is desired in the stomach. In the present study different herbs having anti ulcer property are selected based on the literature survey. Hydroalcoholic extract of Leaves of Aadirachta indica, fruits of Terminalia chebula and Shankha bhasma were used to formulate the floating tablets. HPMCK 100 and Carbopol 934 were used as polymer. Tablets were prepared by wet granulation method. Different pre compression parameters like bulk density, tapped density, angle of repose were measured. Post compression parameters like swelling index, floating lag time, floating time were measured.

KEYWORDS: Polyherbal formulation, Floating tablet, Ulcer.

1. INTRODUCTION
Drug formulation in *Ayurveda* is based on two principles: Use as a single drug and use of more than one drugs, in which the latter is known as polyherbal formulation (PHF). This key traditional therapeutic herbal strategy exploits the combining of several medicinal herbs to achieve extra therapeutic effectiveness, usually known as poly pharmacy or poly herbalism.

Oral drug delivery has always been in the forefront due to ease of administration. However conventional tablets and capsules are not so effective when a longer gastric retention time is desired. Specially in the case of ulcer local delivery of drug is more preferred. To increase the gastric retention time (GRT) of drugs, gastroretentive dosage forms (GRDFs) are developed which can remain in the gastric region for several hours.[1] Prolonged residence time in the stomach is highly desirable for drugs that are locally active in the stomach, or are unstable in the intestinal or colonic environment, and/or have low solubility at higher pH values.[2] Incorporation of the drug in gastroretentive floating dosage form provides a mean to utilize all the pharmacokinetic and pharmacodynamic advantages of controlled release dosage forms.[3]

Gastric ulcer, also known as peptic ulcer, is a localized area of erosion in the stomach lining, resulting in abdominal pain, possible bleeding, and other gastrointestinal symptoms. The most common cause of gastric ulcer is a stomach infection associated with the Helicobacter pylori (*H pylori*) bacteria. The spread of H pylori among humans is not completely understood; it may spread through contaminated food and water. Many people become infected with H pylori at a young age, but symptoms most commonly occur in adulthood.[4]

2. MATERIALS AND METHOD
Fruits of Terminalia chebula and leaves of Azadirachta indica were collected from the local hoseholds of Guwahati. Authenticated in the department of Pharmacognosy, Girijananda Chowdhury Institute of Pharmaceutical Science. Shankha bhasma was procured from BS trading Kolkata, India. Polymers like HPMCK 100, Carbopol 934 and other chemicals used in the experiment were procured from Infinity solution India.

Plant parts were shade dried for 15 days. After that they were subjected to grinding using mechanical grinder. Extraction of the plant material was carried out by simple maceration process by using petroleum ether for 7 days. By this all those fatty material present the plant materials were extracted out. It was followed by soxhlet extraction by using hydroalchoholic solvent. For that 70% ethyl alcohol and 30% water was used. After the extraction was done the concentrated mass of the extract was obtained by rotary evaporator and kept in the refrigerator for further use.

2.1 Determination of foreign matter of raw materials
Plant raw materials were weighed as mentioned below and spreaded it in a thin layer and sorted out of the foreign matter by visual inspection. The portions of these sorted foreign matters were weighed and value in the bulk was calculated per 100 gm of air-dried plant material.

Plant part	Sample size
Terminalia chebula(Fruits)	500 gm
Azadirachta indica(Leaves)	500 gm

2.2 Morphological evaluation of plant raw materials
Morphological evaluation of *Terminalia chebula* (Fruits), *Azadirachta indica* (leaves), and Sankha bhashma were carried out by determining size, shape, colour, order and taste of raw materials.

Preparation of powder from plant raw materials
Plant materials of *Terminalia chebula*, *Azadirachta indica* were powdered separately using a grinder. Powdered plant materials were stored in dry and cool place.

2.3 Physico Chemical Evaluation of Raw materials[5]
2.3.1 Determination of moisture content of raw materials by loss on drying method
Loss on drying method was used for the determination of the water and volatile matter from the two plants. 5 gm of the samples was taken on a tarred evaporating dish and dried the sample in an oven at 105oC for 5 hr separately. Samples were cooled and weighed repeatedly at intervals of an hour until the difference between two successive weighing corresponds to not more than 5 mg.

2.3.2 Total ash
4 gm of the ground air-dried powdered material of Liquorice stolon, Shatavari root, and Amla fruit part were accurately weighed in a previously ignited and tared silica crucible. Material was spreaded in an even layer in crucible and ignited by gradually increasing the heat to above 200°C until material was turn to white colour, indicating the absence of carbon. Crucible was allowed to cool in a desiccator and weighed. Content of total ash was calculated and represented in form of % w/w of air-dried powder material.

2.3.4 Acid insoluble ash
Total ash was prepared by above method. 25ml of 2N HCL was added in crucible which containing total ash. Crucible was covered with a watch-glass and boiled gently for 5 minutes. Watch-glass was rinsed with 5 ml of hot distilled water and this liquid was added into the crucible. Solution was filtered using ashless filterpaper this insoluble matter deposited on an ashless filter-paper was washed with hot distilled water until the filtrate was neutralized. Filter-paper containing the insoluble matter was transferred to the original crucible and ignited in a crucible for 15 minutes at a 430°C temperature. Crucible was allowed to cool in desiccators weighted residue. Acid insoluble ash was calculated and represented in form of % w/w of air-dried powder material.

2.3.5 Water soluble ash
Total ash was prepared by above method. 25 ml of distilled water was added in crucible which containing total ash. Crucible was covered with a watch-glass boiled gently for 5 minutes. Watch-glass was rinsed with 5 ml of hot distilled water and this liquid was added into the crucible. Solution was filtered using ashless filter paper this insoluble matter deposited on an ashless filter-paper was washed with hot distilled water. Filter-paper containing the insoluble matter was transferred to the original crucible and ignited in a crucible for 15 minutes at a 430°C temperature. Crucible was allowed to cool in desiccators weighted residue. Subtract the weight of this residue from the weight of total ash. Water soluble ash was represented in form of % w/w of air-dried powder material.

2.3.6 Alcohol extractive value
10 gm of coarsely powdered air-dried material was weighed and transfered into a glass-stopperd conical flask. Material was macerated with 100 ml of the methanol for 6 hours with shaking frequently and then allows to standing for 18 hours. Extract was filtered rapidly with taking care that not loss any solvent. 25 ml of filtrate was transfered to a tared flat-bottomed evaporating dish. Filtrate was evaporated to dryness on a water-bath. Extract was dried at 105°C for 6 hours and it was cooed in desiccator for 30 minutes and weighed without delay. Alcohol extractable matter was represented in form of % w/w of air-dried material.

2.3.7 Water soluble extractive value
5.0 gm of coarsely powdered air-dried material was weighed and transferred into a glass-Stoppered conical flask. Material was macerated with 100 ml of the distilled water for 6 hours with shaking frequently and then allows to standing for 18 hours. Extract was filtered rapidly with taking care that not loss any solvent. 25 ml of filtrate was transferred to a tared flat-bottomed evaporating dish. Extract was dried at 105°C for 6 hours and it was cooed in desiccators for 30 minutes and weighed without delay. Water extractable matter was represented in form of % w/w of air-dried material.

2.4 Phytochemical investigation of the raw materials[6]
Extraction of Terminalia chebula was performed by using methanol and extraction of Azadirachta indica was performed by using ethanol as solvent. These extracts were then subjected to various qualitative tests for identification of various plant constituents like Total tannins, Total Phenolic, Total Saponin etc.

2.4.1 Test for Alkaloids
For detection of alkaloids, 500 mg of extract was dissolved with 20 ml of HCl (1%) than filter and following test was performed:

2 ml of filtrate, 1 ml of Mayer‟s reagent were added by the side of the test tube. A white or creamy precipitate indicated the test as positive.

2 ml filtrate; 2 ml of Wagner‟s reagent were added by the side of the test tube. A reddish-brown precipitate confirmed the test as positive.

2.4.2 Test for Carbohydrates

Crude extract (400 mg) was dissolved in 20 ml of distilled water and filtered. The filtrate was subjected to following test:

To 2 ml of filtrate, molish reagent was added slowly drop wise along the side of test tube and allowed to stand. A violet ring indicated the presence of carbohydrates.

1 ml of filtrate was boiled on water bath with 1 ml of each Fehling solution A and B. A red precipitate indicated the presence of sugar.

2.4.3 Test for glycosides

For detection of glycoside, 500 mg of extract was dissolved with 20 ml of concentrated HCl than filter and following test was performed: o To 2 ml of filtrate, 3 ml of chloroform was added and shaken, chloroform layer was separated and 10% ammonium solution was added to it. Pink color indicated the presence of glycosides.

2.4.4 Test for Phenolic compounds

2 ml of filtrate, 1-2 drops of 5% FeCl3 solution was added. A dark green color indicated the presence of phenolic compound. 2ml of filtrate, 0.5 ml of lead acetate solution was added. A bulky white precipitate indicated the presence of Phenolic compounds.

2.5.5 Test for Flavanoids

Extract were treated with 3 ml of 2% NaOH solution. Formation of intense yellow color, which becomes colorless on addition of dilute acid (H2SO4), indicates the presence of flavanoids.

3 Quantitative evaluation of raw materials

3.1 Determination of Calcium carbonate content by acid base titration[7]

Acid base titration: 2 gm sankha bhashma was suspended in 50 ml of water followed by the addition of 50 ml 2 N HCL. The mixture was boiled and cooled. Excess HCL was back titrated with 1 N NaOH using bromophenol blue as an Indicator:

3.2 Estimation of total flavonoid content in Neem by Aluminum Chloride Colorimetric Method[8]

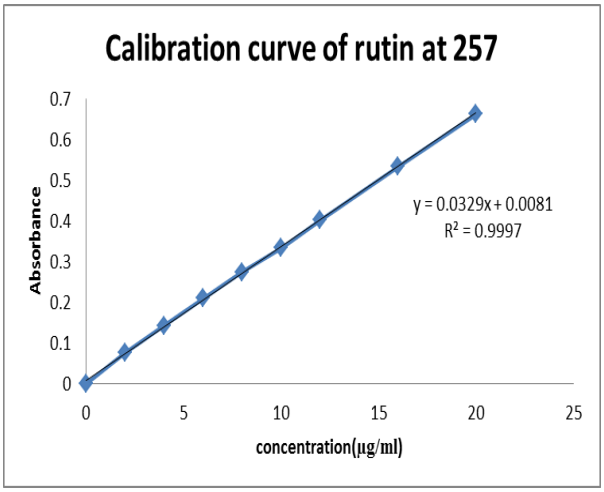

Fig: Calibration curve of rutin.

The determination of the total flavanoid content was carried out based on the aluminum chloride method using rutin as the standard reference. The method was based on the formation of a flavonoid–aluminum complex having the absorption maxima at 415 nm. 100 µl of plant extracts in methanol (10 mg/mL) was mixed with 100 µL of aluminum chloride (20%) in methanol. A drop of acetic acid was added and the mixture was diluted with methanol up to 5 ml. After 40 min the absorbance was measured spectrophotometrically at 415 nm. Blank sample was prepared using 100 µl of methanol in place of plant extract. The absorbance of standard rutin solution (0.5 mg/mL) in methanol was also measured under the same conditions and the total flavonoid content (mg rutin equivalent/mg plant extract) was calculated using the following equation:

Total flavanoid content = $(A \times m_o)/(A_o \times m)$

Where, ‘A’ is the absorbance of plant extract solution, ‘Ao’ is the absorbance of standard rutin solution, ‘m’ is the weight of plant extract, and ‘m_o’ is the weight of rutin in the solution.

3.3 Determination of tannin content by Folin-Ciocalteu reagent method[9]

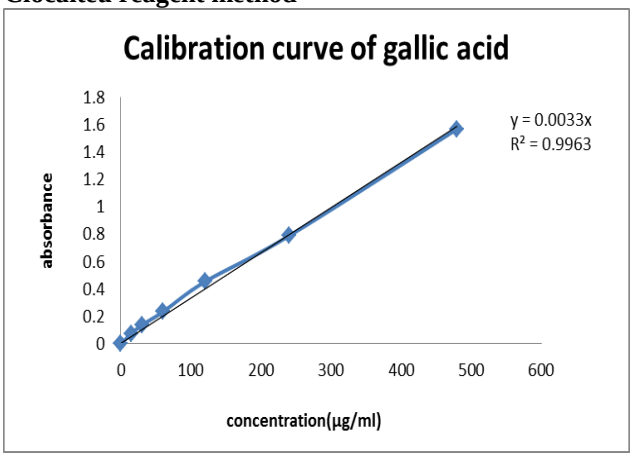

Fig: Calibration curve of gallic acid.

Preparation of FCR reagent: 2 ml of FCR reagent was taken in a beaker and specific water was added for 10 times dilution.

Preparation of standard gallic acid solution
1mg of gallic acid was dissolved in 1 ml of distilled water, so the concentration of the solution is 1mg/ml. The serial dilution was performed in order to prepare different concentrated solution.

Preparation of blank solution
Blank consists of 5ml Folin- ciocalteau reagent, 1ml methanol and 4 ml Sodium carbonate solution

Experimental Procedure
1. 1 ml of plant extract or standard of different concentration solution was taken in a test tube.
2. 5 ml of FC reagent was added into the test tube.
3. 5 ml of Sodium carbonate(7.5%) solution was added into the test tube.
4. Test tube was incubated for 20 minutes at 25˚C to complete the reaction
5. Absorbance of the solution was measured at 760 nm using a spectrophometer against blank.

2.4 Preformulation study[10]

2.4.1 Bulk and Tap density
Both bulk density (BD) and tapped density (TD) was determined as per USP. A quantity of 10 gm of powder blend was introduced in to 25 ml measuring cylinder. After that the initial volume was noted and the cylinder was allowed to fall under its own weight on to a hard surface from the height of 2.5 cm at second intervals. Tapping was continued until no further change in volume was noted. BD and TD were calculated using the following equations.
BD= Weight of the powder blend/Untapped Volume of the packing
TD=Weight of the powder blend/Tapped Volume of the packing

2.4.2 Carr's Index (Compressibility index)
The Compressibility Index of the powder blend was determined by Carr's compressibility index. The formula for Carr's Index is as below:
Carr's Index (%) = [(TD-BD) x100]/BD

2.4.3 Hausner's ratio
The formula for Hausner's ratio is as below:
Hausner's ratio = Tapped density/Bulk density

2.4.5 Angle of repose
The angle of repose of powder blend was determined by the funnel method. Accurately weight powder blend were taken in the funnel. The height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. The powder blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.
tan q = h/r, Where, h and r are the height and radius of the powder cone.

2.4.6 Preparation of Floating Tablet
Floating tablet was prepared by direct compression technique. All the powders were passed through 80 mesh sieve. Required quantity of drug, HPMC K 100m as polymer, Carbopol 934 as polymer, sodium bicarbonate as floating agent, DCP in each formulation were mixed thoroughly. Talc and magnesium stearate were finally added as glident and lubricant respectively. The blend was compressed (12 mm diameter, flat punches) using multipunch tablet compression machine. Each tablet of all three batches contains 75 mg of *Terminalia chebula* fruit extract 65 mg of Azadirachta indica leaf extract, and 30mg shankha bhashma as drug. All extracts of two plants were dissolved in Isopropyl alcohol and this solution was mixed with other polymer(Carbopol and HPMC), DCP and Sodium bicarbonate by gentle mixing in mortar pastel in last Magnesium stearate and talk were added and mixed together. These blends was subjected to direct compression process for formulation of tablet.

Table 1: Formulation of floating tablets with different amount of polymer.

Ingredients	F1(mg)	F2(mg)	F3(mg)	F4(mg)	F5(mg)	F6(mg)	F7(mg)	F8(mg)	F9(mg)
Terminalia chebula Extract	75	75	75	75	75	75	75	75	75
Azadirachta indica Extract	65	65	65	65	65	65	65	65	65
Sankha bhasma	30	30	30	30	30	30	30	30	30
HPMCK100	20	30	40	50	60	70	80	90	100
Carbopol 934	100	90	80	70	60	50	40	30	20
Sodium bi carbonate	115	115	115	115	115	115	115	115	115
Magnesium stearate	8	8	8	8	8	8	8	8	8
DCP	80	80	80	80	80	80	80	80	80
Talc	7	7	7	7	7	7	7	7	7
Total Weight	500	500	500	500	500	500	500	500	500

2.5 Evaluation of the Floating drug[11]

2.5.1 Floating behavior of the tablets (In Vitro buoyancy studies)

The time that tablets took to emerge on the water surface (**floating lag time**) and the time the tablets constantly float on the water surface (**duration of floating**) were evaluated in 250 ml beaker.

2.5.2 Determination of swelling index

The swelling index of tablets was determined in 0.1 N HCl (pH 1.2) at room temperature. The swollen weight of the tablets was determined at predefined time intervals. The swelling index was calculated by the following equation:

Swelling index = (Wt – W0) x 100/ W0

Where, W0 is the initial weight of tablet, and Wt is the weight of the tablet at time t.

2.5.3 Weight variation test

To study weight variation twenty tablets of the formulation were weighed using a Sartorius electronic balance and the test was performed according to the official method.

2.5.4 Hardness

The hardness of five tablets was determined using the Pfizer hardness tester and the average values were calculated.

2.4.5 Thickness

The thickness of the tables was determined by using vernier calipers. Five tablets were used, and average values were calculated.

2.4.6 Friability

The friability of the tablets was measured in a Roche friabilator. Tablets of a known weight (W0) or a sample of 10 tablets are dedusted in a drum for a fixed time (100 revolutions) and weighed (W) again. Percentage friability was calculated from the loss in weight as given in equation as below.

% Friability= (Wo-W)/Wo X100

3. RESULT

3.1 Physicochemical evaluation of raw materials

3.1.2 Determination of moisture content of raw materials by loss on drying method.

Table 2: Moisture content of raw materials.

Sl No	Drug material	Loss on drying
1	Myrobalan	8.7±0.07
2	Neem	7.5±0.05

3.1.3 Determination of Ash value of raw materials

Table 3: Ash value of raw materials.

Sl no	Drug material	Total Ash(%±SD)	Acid insoluble ash	Water soluble ash
1	Myrobalan	2.4±0.15	2.0±0.16	0.65±0.06
2	Neem	1.7±0.05	0.6±0.04	0.4±0.07

3.1.4 Determination of Extractive values of raw materials

Table 4: Determination of extractive value of raw materials.

Sl no	Material	Water soluble extractive value	Alcohol solubleextractive value
1	Myrobalan	24.23±1.23	22.21±1.74
2	Neem	20±0.04	16±0.06

3.2 Phytochemical investigation of raw materials

Table 5: Phytochemical investigation.

Sl no	Test	Azadirachta indica	Terminalia chebula
1	Alkaloid	-	+
2	Carbohydrate	+	+
3	Glycoside	+	+
4	Tannin	+	+
5	Flavanoid	+	+
6	Saponin	+	+

3.3 Quantification of raw materials

Estimation of total tannins from in Myrobalan by Foin- Ciacalteau reagent method

Drug material	Total tannins
Myrobalan	28%

3.3.1 Estimation of total Flavonoid content in Neem by Aluminum Chloride Colorimetric Method.

The total flavanoid content of the Neem leaves by Aluminium chloride colorimetric method was found to be 5mg/gm of the dried extract.

3.3.2 Calcium carbonate content from Sankha bhashma by acid base titration

The calcium carbonate content of the Shankha bhasma was found to be 92%.

3.4 Preformulation studies of powder blend

Table 5: Results of preformulation study.

Batch	Bulk Density(gm/ml)	Tapped Density (gm/ml)	Angle of repose	Carr's index (%)	Hausner's ratio
F1	0.45±0.2	0.53±0.6	23.12±0.7	13.4±0.5	1.15±0.3
F2	0.47±0.1	0.52±1	25.45±1	14.3±0.2	1.34±0.8
F3	0.46±0.5	0.53±0.6	25.55±1.2	14.4±0.5	1.22±0.4
F4	0.44±1	0.54±0.6	25.12±1	13.7±0.8	1.54±0.9
F5	0.46±0.2	0.55±0.7	26.23±0.5	13.5±0.3	1.12±0.3
F7	0.47±0.5	0.53±0.5	26.44±.02	14.2±0.7	1.32±0.8
F8	0.45±0.6	0.55±0.6	27.55±0.4	13.4±1	1.40±0.2
F9	0.46±0.5	0.53±1	28±1	14.4±0.3	1.49±0.8

3.5 Evaluation of floating tablets

3.5.1 Swelling Index

Swelling index of all floating matrix tablets are as shown in the Table below. Concentration of HPMCK100M polymer increased, swelling index was increased.

Fig: In vitro floating study in 0.1 N HCL(F5).

Table 6: **Evaluation parameter for Batch F1 to F9.**

Batch code	Floating lag time(min)	Duration of floating(hr)	Swelling index
1	2	>9	1.45±0.32
2	2.2	>11	1.56±0.43
3	2.4	>12	1.75±0.56
4	2.1	>15	1.87±0.73
5	1.8	>20	2.04±0.43
6	1.9	>20	2.12±0.92
7	1.7	>18	2.22±0.82
8	2.6	>18	2.06±0.52
9	2.5	>18	1.93±0.25

3.5.2 Weight variation
Weight variation data of the prepared tablets indicated no significant difference in the weight of individual tablet from the average value.

3.5.3 Hardness
Hardness of the prepared tablets was observed within the range of 3.8 to 5.4 kg/cm^2.

3.5.4 Thickness
Thickness of floating matrix tablets was found in the range of between 3.1-3.3 mm.

3.5.5 Friability
Friability of tablets was within range.

Table 7: Evaluation of physical parameters for batch F1-F9.

Batch code	Weight variation(%)	Hardness(kg/cm2)	Thickness(mm)	Friability(%)
1	502±6	3.8	3.1±0.3	0.31
2	501±4	4.2	3.2±0.4	0.23
3	498±9	4.3	3.1±0.4	0.18
4	501±5	4.1	3.3±0.3	0.17
5	503±2	4.5	3.3±0.4	0.23
6	501±7	4.7	3.2±0.2	0.18
7	497±4	4.5	3.2±0.5	0.22
8	501±6	5.1	3.1±0.4	0.26
9	502±4	5.4	3.3±0.3	0.18

CONCLUSION

The prepared tablets have shown good floating property and floating lag time. Depending on the concentraton of polymers HPMCK100 and carbopol 934 floating lag time and swelling index of the formulations differed. Formulation 5 and 6 showed floating time for more than 20 hours. An optimum concentration of the polymer is needed to show good floating property. Swelling index is also varied depending on the polymer concentration. Formulation 7 showed both good swelling index and floating property. Which is more than 18 hours. Floating lag time also decreased in the formulation 7. This shows that the both the polymer ratio have also contributed to the floating lag time of the tablets.

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