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Formulation floating tablet of from aqueous extract of *Acacia* and its evaluation

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Abstract
Introduction: Floating tablets prolong the gastric residence time of drugs, improve bioavailability, and facilitate local drug delivery to the stomach. With this objective, floating tablets containing aqueous extract of acacia as drug was prepared for the treatment of *Helicobacter pylori* and gastric ulcers.
Methods: The aqueous extract of acacia was standardized by TLC. Tablets containing HPMC, Acacia extract, sodium bicarbonate (gas generating agent), talc, and magnesium stearate were prepared using direct compression method. The formulations were evaluated for physical parameters like diameter, thickness, hardness, friability, uniformity of weight, drug content, buoyancy time, dissolution, and drug release mechanism. The formulations were optimized on the basis of buoyancy time and *in vitro* drug release.
Results: The diameter of all formulations was in the range 11.2-11.85mm; thickness was in the range 3.95-4.09 mm. The hardness ranged from 4 to 4.5 kg/cm [2]. All formulations passed the USP requirements for friability and uniformity of weight. The buoyancy time of all tablet formulations was less than 5 min and tablet remained in floating condition throughout the study.
Conclusion: The optimized formulation was found to be F6 which released 98.4% of drug in 11 h *in vitro*, while the buoyancy time was 3.5 min.

Keywords: *Acacia*, floating, ulcer

Introduction
Oral controlled release dosage forms have been developed over the past three decades due to their considerable therapeutic advantages such as ease of administration, patient compliance, and flexibility in formulation. However, this approach has several physiological difficulties such as inability to restrain and locate the controlled drug delivery system within the desired region of the gastrointestinal tract (GIT) due to variable gastric emptying and motility. Gastroretentive dosage form can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility of drugs that are less soluble in a high pH environment. The types of gastroretentive dosage forms are floating drug systems – effervescent and no effervescent systems [1].
Polyphenols are the class of chemical compounds synthesized by fruits, vegetables, teas, cocoa and other plants that possess certain health benefits. They are an integral part of human diet and responsible for overall organoleptic properties of plant foods. Plant polyphenols have drawn increasing attention due to their potent antioxidant properties and their marked effects in prevention of various oxidative stress associated diseases such as cardiovascular, cancer and neurodegenerative diseases [2-6] Catechin, a flavonol is a polyphenolic compound found in tea, coca and several fruits. The terminal three leaves of the Camellia plant is used for the production of green, black tea. The green tea contains 30 to 50% polyphenols [7]. Mainly epicatechin, epicatechin gallate, epigallocatechin and epigallocatechin gallate on the dry weight basis [7, 8]. They constitute 90% of the total flavonoids [9] and a cup of green tea contains about 150 to 210 mg of polyphenol [10]. In black tea, catechins are converted to the flavines [7-

[11]. Many researchers have demonstrated that the phytochemicals present in tea have beneficial effect as they act as a free radical scavenger. They have shown strong antioxidant activity like vitamin C, E and carotenoids [12], anti-inflammatory [13], cholesterol lowering [14], antiulcer effect, antiviral and antibacterial acitivites [14, 15].

Drug Delivery Systems

Controlled Drug Delivery Systems

Controlled drug delivery systems have been developed which are capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity and/or targeting the delivery of drug to a tissue [16]. Controlled drug delivery or modified drug delivery systems are conveniently divided into four categories.

1) Delayed release
2) Sustained release
3) Site-specific targeting
4) Receptor targeting

Oral Controlled Drug Delivery Systems

Oral controlled release drug delivery is a drug delivery system that provides the continuous oral delivery of drugs at predictable and reproducible kinetics for a predetermined period throughout the course of GI transit and also the system that target the delivery of a drug to a specific region within the GI tract for either local or systemic action.

Gastroretentive Dosage Form (GRDF) [17-18]

It is evident from the recent scientific and patient literature that an increased interest in novel dosage forms that are retained in stomach for a prolonged and predictable period of time exists today in academic and industrial research groups. One of the most feasible approaches for achieving a prolonged and predictable drug delivery in the GI tract is to control the gastric residence time (GRT), i.e. gastro retentive dosage form (GRDFs or GRDS). GRDFs extend significantly the period of time over which the drugs may be released. They not only prolong dosing intervals, but also increase patient compliance beyond the level of existing controlled release dosage form.

Need for gastroretentive drug delivery system [19]

Various drugs have their greatest therapeutic effect when released in the stomach, particularly when the release is prolonged in a continuous, controlled manner. Drugs delivered in this manner have a lower level of side effects and provide their therapeutic effects without the need for repeated dosages or with a low dosage frequency. Sustained release in the stomach is also useful for therapeutic agents that the stomach does not readily absorb, since sustained release prolongs the contact time of the agent in the stomach or in the upper part of the small intestine, which is where absorption occurs and contact time is limited. Under normal or average conditions, for example, material passes through the small intestine in as little as 1-3 hours.5 In general, appropriate candidates for CRGRDF are molecules that have poor colonic absorption but are characterized by better absorption properties at the upper parts of the GIT. Dosage form with prolonged GRT, i.e. gastro retentive dosage form (GRDF), will bring about new and important therapeutic options such as:

1. This application is especially effective in sparingly soluble and insoluble drugs. It is known that, as the solubility of a drug decreases, the time available for drug dissolution becomes less adequate and thus the transit time becomes a significant factor affecting drug absorption. To override this problem, erodible, gastroretentive dosage forms have been developed that provide continuous, controlled administration of sparingly soluble drugs at the absorption site.
2. GRDFs greatly improve the pharmacotherapy of the stomach through local drug release, leading to high drug concentration at the gastric mucosa. (For e.g. Eradicating Helicobacter pylori from the submucosal tissue of stomach) making it possible to treat stomach and duodenal ulcers, gastritis and oesophagitis, reduce the risk of gastric carcinoma and administer non-systemic controlled release antacid formulations (calcium carbonate).
3. GRDFs can be used as carriers for drugs with so called absorption windows. These substances for e.g. antiviral, antifungal and antibiotic agents (Sulphonamides, Quinolones, Penicillins, Cephalosporins, Aminoglycosides, Tetracyclines etc.) are taken up only from very specific sites of the GI mucosa.

Approaches to Gastric Retention [20, 21]

Buoyant/ Floating Systems

Floating Drug Delivery Systems (FDDS) have a bulk density lower than gastric fluids and thus remain buoyant in the stomach for a prolonged period of time, without affecting the gastric emptying rate while the system is floating on the gastric contents, the drug is released slowly at a desired rate from the system. After the release of the drug, the residual system is emptied from the stomach. This results in an increase in the GRT and a better control of fluctuations in the plasma drug concentrations. Floating systems can be classified into two distinct categories, non-effervescent and effervescent systems.

Mechanism of floating systems [22]

Various attempts have been made to retain the dosage form in the stomach as a way of increasing the retention time. These attempts include introducing floating dosage forms (gas generating systems and swelling or expanding systems), mucoadhesive systems, high-density systems, modified shape systems, gastric-emptying delaying devices and co administration of gastric emptying delaying drugs. Among these, the floating dosage forms are the most commonly used. Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affectingthe gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is eliminated from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration. However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention effect, a minimal level of floating force (F) is also required to maintain the buoyance of the dosage form on the surface of the meal. To measure the floating force kinetics, a novel apparatus for determination of resultant weight has been reported in the literature. The apparatus operates by measuring continuously the force equivalent to F (as a function of time) that is required to maintain a submerged object.

$$F = F_{buoyancy} - F_{gravity} = (Df - Ds)\, gv$$

Where,

F= total vertical force, Df = fluid density,

Ds = object density, v = volume and
g = acceleration due to gravity.

Types of Floating Drug Delivery Systems (FDDS) [23, 24]
Based on the mechanism of buoyancy, two distinctly different technologies have been utilized in development of FDDS which are: A. Effervescent System, and B. Non- Effervescent System.

Advantages of FDDS:
Floating dosage systems form important technological drug delivery systems with gastric retentive behavior and offer several advantages in drug delivery. These advantages include:

1. Improved drug absorption, because of increased GRT and more time spent by the dosage form at its absorption site.
2. Controlled delivery of drugs.
3. Delivery of drugs for local action in the stomach.
4. Minimizing the mucosal irritation due to drugs, by drug releasing slowly at controlled rate.
5. Treatment of gastrointestinal disorders such as gastro-esophageal reflux.
6. Simple and conventional equipment for manufacture.
7. Ease of administration and better patientcompliance.
8. Site-specific drug delivery.

Materials:
Acacia catechu extract, hydroxy propyl methyl cellulose (HPMC), carbopol, Psyllium husk, Sodium bicarbonate, Micro crystalline cellulose (MCC), Citric acid, Magnesium stearate, talc

Materials and Method

Materials
The leaves and steam of the plant *Acacia catechu* were purchased from local market in Karjat, India. Hydroxy propyl methyl cellulose (HPMC), carbopol, Microcrystalline cellulose (MCC) was obtained from Sigma aldrich Laboratory, USA. Sodium bicarbonate was obtained from SR Research Laboratories Pvt. Ltd., Mumbai. Talc was obtained from Loba, Mumbai. Magnesium stearate was obtained from Loba, Mumbai. Catechin was procured from Sigma Aldrich Inc., USA. Chloroform was obtained from Nice Chemicals Pvt. Ltd., Cochin. Formic acid was obtained from Chemicals Pvt. Ltd., Cochin. Acetone, diethyl ether, and methanol were obtained from Merck Specialties Pvt. Ltd., Mumbai. All chemicals used were of analytical and pharmaceutical grade.

Formulation of tablets
In the present study, all the tablets were formulated by direct compression technique using polymer like HPMC and other ingredients like carbopol, magnesium stearate, talc, and sodium bicarbonate. All ingredients were passed through sieve no # 80 and weighed accurately on electronic balance. The extract, HPMC, sodium bicarbonate, and carbopol were mixed properly in a mortar and pestle to get a uniform tablet blend. Finally talc and magnesium stearate were mixed with the blend. The tablet blend was then weighed individually according to the formula and compressed into tablets using single punch tableting machine. The different formulations were labeled F1-F7 and their formulae are given in Table No.1.

Table 1: Composition of floating tablet formulations

Ingredients	F1	F2	F3	F4	F5	F6	F7
Acacia catechu Extract	200	200	200	200	200	200	200
HPMC	100	95	90	85	80	75	70
Carbopol	35	40	45	50	55	60	65
$NaHCO_3$	50	50	50	50	50	50	50
MCC	50	50	50	50	50	50	50
Citric Acid	25	25	25	25	25	25	25
Lactose	25	25	25	25	25	25	25
Mg Stearate	5	5	5	5	5	5	5
Talc	10	10	10	10	10	10	10

Evaluation of floating tablets
The prepared floating tablets were evaluated for diameter and thickness using Vernier calipers. The hardness of the tablets was evaluated using a Monsanto hardness tester. The friability was determined in a Roche friabilitor. Twenty tablets from each formulation were weighed and their average weight was determined Table No.2.

Table 2: Evaluation of formulated tablets

	Thickness	Hardness (kg/cm^2)	Wt. Variation (mg)	Friability (%)	Drug Content (%)	% drug release In 12 hrs	Buoyancy Lag time(Sec)	Total Flotation time(Hrs)
F1	3.95±0.05	5.21±0.28	508±2.32	0.61	98.45	78.21±1.98	88±3	11
F2	3.98±0.02	4.55±0.28	495±4.37	0.29	97.99	72.32±2.93	59±2	10
F3	4.05±0.07	4.77±0.28	502±1.08	0.52	99.05	89.03±3.21	79±5	12
F4	3.99±0.10	4.30±0.28	498±2.31	0.21	98.06	98.11±0.56	68±1	13
F5	4.11±0.09	4.95±0.28	506±5.47	0.39	96.79	81.39±1.13	73±4	11
F6	4.01±0.03	4.77±0.28	501±0.38	0.49	96.56	90.51±3.11	86±3	12
F7	3.97±0.06	5.02±0.28	492±7.86	0.78	97.64	92.79±2.31	72±6	12

Buoyancy time
The time taken for dosage form to emerge on surface of medium called floating lag time (FLT) or buoyancy lag time (BLT). Floating behavior studies were performed in a USP type II (paddle) apparatus at speed 100 rpm in 900 mL 0.1N HCl at 37 ± 0.2 °C to mimic *in vivo* conditions. FLT was determined on the basis of visual inspection [25].

In vitro dissolution studies

The in vitro dissolution studies were carried out using USP type I (basket) apparatus. The dissolution medium was 900 mL 0.1N HCl. The dissolution medium was kept in thermostatically controlled water bath, maintained at 37±0.5 °C. The tablet was placed into the basket. The speed of rotation was kept at 100 rpm. At different time intervals, 5 mL of sample was withdrawn and dissolution medium was kept constant throughout by replacing with equal volume 5 mL of dissolution medium. The aliquots were extracted with 30 mL of chloroform and the chloroform fraction was analyzed spectrophotometrically at 276 nm against blank chloroform for drug release. The study was performed in triplicate [25].

Results

Evaluation of formulated tablets

The thickness of all formulations was in the range 3.95-4.11 mm. The hardness ranged from 4.30-5.21 kg/cm^2. All formulations passed the USP requirements for friability and uniformity of weight Table No.2

Buoyancy lag time

The buoyancy lag time of formulations are shown in Table No.2 FLT of all formulations was found to be less than 2 min. The carbon dioxide generated from sodium bicarbonate upon contact with the acidic medium will remain entrapped in the gellified layer of the swollen polymer (hydrocolloids). This produces an upward motion of the dosage form and maintains its buoyancy. The FLT may be explained as a result of the time required for dissolution medium to penetrate the tablet matrix and develop the swollen layer for entrapment of CO_2 generated *in situ*. The tablet mass decreased progressively due to liberation of CO_2 and release of drug from the matrix. On the other hand, as solvent front penetrated the glassy polymer layer, the swelling of HPMC caused an increase in volume of the tablet. The combined effect is a net reduction in density of the tablets, which prolongs the duration of floatation beyond 12 h.

All formulations found to content more than 99% of the drug. During formulation development, the ingredients used were selected based on the approach of achieving drug release for 12 h. Floating drug delivery is based on the swelling property and density of the polymers as well as the gas generating agent [26]. The work was started using carbopol which swells to a greater extent [27]. Sodium bicarbonate was used as a gas-generating agent, which reacts with the gastric fluids and produces carbon dioxide. This gas is entrapped into swollen matrix and provides buoyancy to the formulation [26]. HPMC having high viscosity and ability to swell was used.

In vitro drug release. In this work, we have carried out in vitro drug studies in 0.1N HCl as the dissolution medium to study the drug release of the tablet formulations. Varying concentration of HPMC and Carbopol was used for different formulations F4 found to retard the drug release for longer time.

Optimization of tablet formulation

The buoyancy lag time of all formulations was in the range 59 to 88 sec. Based upon the flotation time and % cumulative drug release formulations were optimized. The % cumulative drug release was in the range 72-98%. The optimized formulation was found to be F4. The buoyancy time was 68 sec and % cumulative drug release was 98.11%.

Conclusion

Floating tablets of *Acacia extract*, HPMC, carbopol, talc, sodium bicarbonate, and magnesium stearate were prepared. Formulated tablets were within acceptable limits for various physicochemical evaluations for tablets like tablet dimensions, hardness, uniformity of weight, friability, buoyancy time, and in vitro drug release. *In vitro* dissolution studies for the floating tablets were carried out in 0.1N HCl at 37 °C. About 72-98% of the drug was released in 12 h. Formulation F4 showed good floating behavior along with better--controlled drug release in comparison to other prepared formulations. We can conclude that carbopol, sodium bicarbonate and HPMC in combination can be promising polymers for gastroretentive drug delivery systems. Floating tablets of aqueous extract of *Acacia catechu* can be formulated as an approach to increase gastric residence time, thereby improving its bioavailability. The results indicate a promising potential of aqueous extract of *Acacia catechu* floating tablets as an alternative to the conventional dosage form.

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