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Enhancing Gastric Retention: A Novel Gastroretentive Drug Delivery System Utilizing Punica granatum and Jackfruit Seed as Polymer.

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ABSTRACT

Oral drug delivery is widely preferred for its ease of use, affordability, and patient compliance. However, challenges like enzymatic degradation, gastric pH variations, and inconsistent gastrointestinal transit can hinder drug absorption. Gastroretentive drug delivery systems (GRDDS), particularly floating drug delivery systems (FDDS), help overcome these issues by prolonging gastric retention and enabling controlled drug release.

With the growing interest in phytopharmaceuticals, research has expanded into natural bioactive compounds. Pomegranate (*Punica granatum L.*) offers antiviral, antibacterial, antifungal, antioxidant, and anti-inflammatory benefits due to its polyphenol content. Jackfruit (*Artocarpus heterophyllus Lam.*) seeds contain bioactive compounds with anticancer, antihypertensive, and antiulcer properties, while also serving as a natural binder in formulations. This study explores the incorporation of pomegranate and jackfruit seed extracts into GRDDS, aiming to enhance drug bioavailability and therapeutic efficacy, contributing to the development of herbal-based pharmaceutical innovations.

INTRODUCTION

Oral drug delivery is simple, natural, and non-invasive, it is the most widely used form of administration. Because of its ease of use, it is regarded as the most practical and patient-friendly medication delivery method[1]. It is a feasible choice for a variety of therapeutic applications due to its cost-effective manufacturing technique and versatility in formulation design. The oral route's extensive use in clinical practice is further supported by its low risk and low complications[2].

Additionally, physiological challenges like stomach pH and activity of enzymes, as well as variations in movement of the gastrointestinal tract, might make it more difficult for the medication to be released and absorbed uniformly[3]. These difficulties have prompted the development of sustained and controlled release systems, which modify the release profile in order to maintain a steady amount of medication at the site of absorption for several hours[4]. These systems lower the frequency of use and the possibility of side effects linked to peak concentrations while increasing bioavailability, minimizing medication plasma level swings, and improving therapeutic outcomes[5].

The two main objectives of developing prolonged to regulate release systems are to maintain long-term, effective blood levels of medication and to facilitate the drug's gradual release in the gastrointestinal tract (GIT)[6]. In the upper GIT, longer stomach retention durations enable site-specific drug release for both local and systemic therapeutic advantages. Gastroretentive medication delivery technologies permit this. To achieve this, numerous methods have been proposed to enhance the retention of dosage forms in the stomach, including bioadhesive mechanisms, swelling and extending systems, and floating systems. Floating systems for drug delivery, also called hydrodynamically balanced systems, have sufficient buoyancy to keep floating on the contents of the stomach. This allows them to remain suspended in the stomach without significantly altering the pace of gastric emptying, which guarantees prolonged gastric retention[7,8].

The demand for phytopharmaceutical pharmaceuticals and the active ingredients in Ayurvedic remedies is rising in India and other parts of the world, particularly in Western markets. Natural products are becoming more and more valuable as a source of novel bioactive chemicals. The therapeutic power of plants has long been recognized by traditional medical systems, particularly Ayurveda. Ayurvedic medicine has utilized extracts from a wide range of plant parts, such as bark, roots, leaves, delicate stems, fruits, and flowers, to treat a wide range of chronic ailments[9].

The pomegranate, or *Punica granatum* L., is one fruit with important therapeutic uses. Due to the biological compounds (active molecules) found in the various fruit parts, several of the fruit's components have been shown to have antiviral, antibacterial, antifungal, hypolipidemic, anticarcinogenic, anti-inflammatory, antioxidant, and antiatherosclerotic properties[10]. Polyphenols like punicalagin, which is abundant in antioxidants, are found in pomegranate peel. Additional polyphenols consist of flavonols and anthocyanins (delphinidin, cyanidin, and pelargonidin 3-glucosides and 3,5-glucosides)[11]. Pomegranate fruit contains chemicals that have been shown to have anti-

inflammatory qualities by Lee CJ et al. Pomegranate chemicals have been shown in in vitro experiments to have anti-inflammatory qualities[12,13].

Jackfruit seeds, which are wild in the forest and contain lignans, isoflavones, saponins, and other phytonutrients, have a wide range of health advantages, including anticancer, antihypertensive, antiaging, antioxidant, and antiulcer properties[14]. Jackfruit seed powder has binding and thickening qualities. Jackfruit, or *Artocarpus heterophyllus* Lam, is a member of the Moraceae family. It is Bangladesh's national fruit[15,16].

The current study's goal is to create and assess tablets with *Artocarpus heterophyllus* seed powder as an excipient. Pomegranate peel extract was employed as the study's model medication.

MATERIAL AND METHOD:

Plant Material and Extraction:

The farm was the source of the pomegranates (*Punica granatum*). The Kharavate-based S.P. College of Agriculture verified the sample. The peel was separated by hand, allowed to dry in the sun, and then ground into a powder. The powder underwent a 36-hour extraction process using methanol and a Soxhlet extractor. After using an electric water bath to concentrate the resulting methanolic extract, a semisolid, sticky extract was produced.

In the Ratnagiri district of Maharashtra, India, the Jackfruit (Artocarpus heterophyllus) was selected from the surrounding environment. The collected fruit was authenticated by S.P.College of Agriculture, Kharavate. other excipients like Magnesium sterate, Talc were purchased from Loba chemicals, Mumbai.

Method of preparation:

Six different formulations of non-effervescent floating tablets containing peel extract from Punica granatum were made using the direct compression method. Lactose, magnesium stearate, talc, Artocarpus heterophyllus seed extract, and Hydroxypropyl Methyl Methylcellulose K100M (HPMC K100M) were among the excipients utilized in the formulations. An analytical balance was used to precisely weigh the raw components, and each component was then sieved through a 40-mesh screen to guarantee consistency. To create a uniform powder, the medication (Punica granatum peel extract), lactose, HPMC K100M, and Artocarpus heterophyllus seed extract were manually mixed in a mortar and pestle. Talc and magnesium stearate were then added as lubricants to help with the compression process. A rotary tablet press was used to compress the final powder combination into tablets[17,18]. Each formulation, denoted as F1 through F6, is described in full in Table 1.

Table No. 1 Formulation Table

Ingredients	Role	F1	F2	F3	F4	F5	F6
Punica granatum peel extract	API	200 mg	200 mg	200 mg	200 mg	200 mg	200 mg
HPMC K100M	Polymer	70 mg	80 mg	90 mg	--	--	--
Artocarpus heterophyllus Seed extract	Polymer	--	--	--	70 mg	80 mg	90 mg
Lactose	Diluent	50 mg	40 mg	30 mg	50 mg	40 mg	30 mg
Magnesium Stearate	Lubricant	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg
Talc	Glidant	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg

Pre-compression studies:

The pre-compression parameters of the formulations meant for compression were assessed in order to evaluate the powders flow characteristics. These characteristics included the compressibility index, Hausner's ratio, bulk density, tapped density, and angle of repose[19].

Angle of Repose[20]

The funnel method was used to find the angle of repose. Until the maximum cone height (h) was reached, the powder was permitted to pass through a funnel that was progressively increased vertically. After determining the radius of the created heap (r) and using the inverse tangent of the height to radius ratio, the angle of repose was determined. Using the following formula, the angle of repose (Θ) was determined:

Θ = tan-1 (h/r)

Bulk Density and Tapped Density[18]

After adding 10 g of powdered sample to a dry, clean measuring cylinder, the volume (V0) that the sample occupied without tapping was calculated. The cylinder was then dropped from a height of one inch onto a hard hardwood surface at intervals of two seconds until the powder occupied a consistent volume (Vt). These numbers were used to calculate the bulk and tapped densities.

Bulk density is calculated as follows: powder weight (w) divided by powder bulk volume (V0). Tapped density is calculated by dividing the powder's weight (w) by its tapered volume (Vt).

Carr's Index

The formula was used to determine Carr's index, or the powder's compressibility index.

Carr's Index= [(Tapped density-Bulk density)/Tapped density] * 100

Hausner Ratio

The formula was used to determine the Hausner Ratio.

Hausner Ratio=Tapped density/Bulk density

Post compression studies:

Each batch underwent a separate post-formulation evaluation, which included testing for thickness, diameter, weight fluctuation, and friability. Six formulations were also subjected to in vitro buoyancy and dissolving testing[21].

Thickness and diameter measurement[22]

A Vernier caliper will be used to measure each tablet's thickness and diameter after a sample of 20 has been chosen.

Weight Variation

Individual tablet weight variation is a reliable predictor of the corresponding variance in medication content. Using a digital analytical balance, 20 tablets will be weighed separately to establish the average weight of the tablets.

Friability Test:

The friability of the tablets was evaluated using a Roche Friabilator and expressed as a percentage (%). Initially, ten tablets were weighed (W) and transferred into the friabilator. The friabilator was operated at 25 rpm for 4 minutes or until it reached 100 revolutions. Afterward, the tablets were weighed again (Wo). The percentage of friability was then calculated using the formula:

%F = 100 (1-Wo/W)

Tablets with a friability of less than 1% were deemed desirable.

Buoyancy lag time[23]

The amount of time it takes for the tablet to float and ascend to the surface is known as the buoyancy lag time. The tablets buoyancy was assessed in 900 milliliters of simulated stomach fluid at 37±0.5 ºC. A stopwatch was used to measure the

buoyancy lag time, and a visual observation was made of the total floating time.

Floating time[24]

Throughout the investigation, 900 mL of 0.1N HCl was kept at 37±0.5ºC and a IP dissolving apparatus I was used to quantify the floating time at 50 rpm. The time it takes for the tablet to rise to the surface, known as the floating lag time, and the time it stays afloat in the dissolving solvent are both included in the overall floating time. Visual inspection was used to evaluate this.

Dissolution Test:

Utilizing the IP equipment I dissolution equipment, dissolution investigations were conducted. Punica granatum peel methanolic extract tablets were kept at 37 ± 0.5°C and agitated with a paddle at 50 rpm in a dissolution vessel filled with 900 mL of 0.1N hydrochloric acid (pH 1.2). The dissolving media was changed out for new samples at prearranged intervals. Once the methanolic extract was filtered via Whatman filter paper, its concentration was measured using spectrophotometry at 227 nm. Every investigation was carried out in duplicate[25].

Results:

Pre-compression studies:

To investigate the flow characteristics of powders, pre-compression parameters (repose angle, tapped density, bulk density, Hausner's ratio, and compressibility index) were applied to formulations made for compression. Table 2 provides a description of the findings.

Table No. 2 Precompression parameters of powders

Post compression parameters:

Formulation code	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's compressibility index (%)	Hausner's ratio	Angle of repose(°)
F_1	0.35	0.44	20.45	1.25	31.79
F_2	0.42	0.52	19.13	1.23	27.389
F_3	0.33	0.39	15.38	1.18	30.96
F_4	0.33	0.44	25	1.33	23.742
F_5	0.42	0.50	16	1.19	24.62
F_6	0.47	0.53	11.32	1.12	28.96

Following compression, a variety of metrics were assessed, including thickness, diameter, weight fluctuation, and friability. Table 3 provides a description of the results.

Table No. 3 Tablet characteristics of different formulation

Formulation code	Average weight (gm)	Thickness (mm)	Friability (%)
F1	0.354±0.3	4.00±0.02	0.40±0.12
F2	0.349±0.02	4.00±0.05	0.45±0.15
F3	0.351±0.05	4.00±0.03	0.50±0.18
F4	0.356±0.05	4.00±0.01	0.40±0.09
F5	0.353±0.08	4.00±0.07	0.30±0.15
F6	0.352±0.08	4.00±0.02	0.20±0.15

In vitro buoyancy studies:

Every tablet formulation was made using a non-effervescent method. Tablets in vitro buoyancy in 0.1 N HCl was assessed and Table 4 displays the findings.

Table No. 4 In vitro buoyancy studies of different formulation

Formulation code	Buoyancy Lag Time (min)	Floating Time (hours)
F_1	5 min 05Sec	>12
F_2	4 min 50 Sec	>12
F_3	4 min 20 sec	>12
F_4	4 min 05 Sec	>12

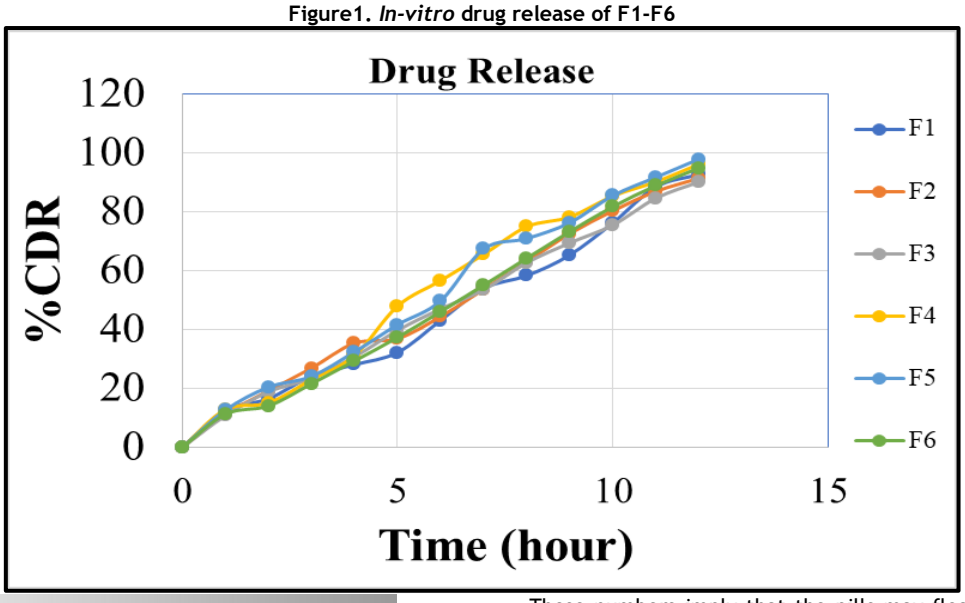
F_5	3 min 20 Sec	>12
F_6	3 min 10 Sec	>12

In vitro dissolution studies:
Using a IP class I dissolution apparatus (paddle apparatus), in vitro dissolution tests were conducted in 0.1 N HCl (pH 1.2). In table 5, the effects of different components and their concentrations on medication release are examined.

Table No. 5 Drug Release of Methanolic Extract of *Punica granatum* peel Tablet

Sr. No.	Time	Formulation					
		F1	F2	F3	F4	F5	F6
1.	0 min	0	0	0	0	0	0
2.	1 hour	12.60%	11.19 %	10.79 %	12.86%	12.65 %	11.29%
3.	2 hours	16.53%	19.23 %	18.88%	15.14 %	20.44 %	14.09%
4.	3 hours	24.17%	26.94 %	23.47%	23.04 %	24.15 %	21.61%
5.	4 hours	28.13%	35.41 %	30.81%	31.16 %	32.46 %	29.38%
6.	5 hours	32.23%	36.95 %	39.77%	48.01 %	41.68 %	37.38%
7.	6 hours	43.17%	44.46 %	47.06%	56.67 %	49.79 %	46.14%
8.	7 hours	54.05%	53.72 %	53.53%	65.56 %	67.40 %	55.09%
9.	8 hours	58.36%	63.11 %	62.77%	74.98 %	70.97 %	64.26%
10.	9 hours	65.37%	72.60 %	69.47%	78.29%	76.35 %	73.30%
11.	10 hours	76.29%	80.38 %	75.52%	85.39 %	85.52 %	81.80%
12.	11 hours	88.50%	86.96 %	84.67%	90.23%	91.78 %	88.91%
13.	12 hours	92.73%	91.42%	90.19%	95.22%	96.95 %	94.92%

Figure1. *In-vitro* drug release of F1-F6



DISCUSSION

According to the tablet formulations' precompression parameters, the tapped density varied between 0.39 and 0.53 g/mL, and the bulk density ranged between 0.33 and 0.47 g/mL. These numbers imply that the pills may float in stomach juice. Other micromeritic features, such as the Hausner's ratio and Carr's index, did not exhibit any notable changes. Favorable flow characteristics were indicated by the angle of repose, which

ranged from 23.74° to 31.79°. All of the tablet's characteristics, including thickness, weight fluctuation, hardness, and friability, fell within reasonable bounds.

The buoyancy lag time varied between 3 minutes and 10 seconds to 5 minutes and 5 seconds, and the floating time exceeded 12 hours for all formulations. These findings suggest that the formulations were stable and complied with the limits specified by the Indian Pharmacopoeia. Detailed results are provided in the table.

All formulations exhibited consistent floating behavior in the dissolution medium, and their buoyancy capacities were recorded. Formulations F1 to F3, which contained the synthetic polymer HPMC K100 M, maintained floatation for more than 12 hours. In contrast, formulations F4 to F6, which contained the natural polymer *Artocarpus heterophyllus* seed extract, exhibited extended floatation times compared to the synthetic polymer-based formulations. These results suggest that the natural polymer-based formulations provided superior buoyancy in the dissolution medium.

The In-vitro drug release profiles for formulations F1-F6, which utilized both natural and synthetic polymers, are presented in Table 5. Cumulative percentage drug release versus time (hours) for these formulations is illustrated in Figure. The synthetic polymer formulation F1 exhibited a higher release of 90.19% over 12 hours, while the natural polymer formulation F5 demonstrated an even higher release of 96.95% during the same period. Among all formulations (F1 to F6), F5 exhibited the best cumulative drug release at 96.95% over 12 hours. Considering all evaluation parameters, F5 was selected as the best formulation.

CONCLUSION

Based on the findings of this study, it can be concluded that the floating tablets utilizing *Artocarpus heterophyllus* seed extract (jackfruit) in optimized concentration can be used to increase the GRT of the dissolution fluid in the stomach to deliver the drug in a controlled manner. The concept of formulating floating tablets of *Punica granatum* peel extract offers a suitable and practical approach in serving desired objectives of gastro retentive floating tablets.

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