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Formulation and Evaluation of Gastroretentive Floating Tablets of Diltiazem Hydrochloride

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ABSTRACT

The objective of this research was to create an innovative gastroretentive drug delivery system utilizing the wet granulation technique for the sustained clemency of the active agent. Rapid gastrointestinal transit may lead to incomplete API clemency from the delivery system above the absorption zone, resulting in reduced efficacy of the administered dose and consequently lower patient compliance. Gastroretentive floating tablets were designed to ensure the desired sustained and complete API clemency over an extended period. Floating tablets of Diltiazem were formulated proving the wet granulation mode with varying concentrations of Gum Kondagagu, Gum Olibanum, and Locust Bean Gum. The optimized formulation (DF14) demonstrated an API release of 99.54% within 12 hours, with a buoyancy lag time of 33 seconds. In vitro API clemency kinetics indicated adherence to both zero-order kinetics, and the potential mechanism for the release of Diltiazem Hydrochloride from the optimized formulation may be linked to the super case II transport mechanism. The optimized formulation (DF14) exhibited no significant alterations in physical appearance, drug content, floating lag time, or in vitro dissolution modules after being subjected to 75%±5% relative humidity at 40±2°C for a duration of 6 months.

KEY WORDS: Wet granulation, Floating lag Time, Gastroretentive, Diltiazem Hydrochloride.

INTRODUCTION

Oral administration is widely regarded as the most convenient and preferred route for delivering drugs into systemic circulation. In recent years, there has been growing interest in oral controlled-release drug delivery systems within the pharmaceutical industry. These systems offer several therapeutic benefits, including simplified dosing schedules, improved patient adherence, and enhanced formulation versatility. Short half-lives are quickly cleared from the bloodstream, requiring frequent dosing to maintain therapeutic levels[1]

Following oral administration, certain drug delivery systems are designed to remain in the stomach and release the drug in a controlled fashion, ensuring a continuous supply to the primary absorption sites within the gastrointestinal (GI) tract. However, these systems often face challenges such as a short gastric retention time (GRT) and variable gastric emptying time (GET), which can result in the drug leaving the stomach prematurely. This may lead to incomplete release in the targeted absorption area—typically the stomach or the upper small intestine—reducing the drug's overall effectiveness. To enhance site-specific drug delivery through the oral route, it is important to prolong the drug's residence time in the stomach. Extended gastric-retention can enhance bioavailability, sustain drug release, minimize drug loss, and improve the solubility of drugs that are poorly soluble in higher pH environments.

A key challenge in developing oral controlled-release drug delivery systems (CRDDS) is maintaining the drug's therapeutic action over an extended period, especially once it passes into the small intestine. For optimal

performance, the drug should ideally exhibit consistent absorption throughout the GI tract, preferably via passive diffusion.[2]

Diltiazem is an antihypertensive and vasodilating agent that works by relaxing the vascular muscle and reducing blood pressure. This is related to the long-term therapeutic effects, as lowering the blood pressure reduces the risk of fatal and non-fatal cardiovascular events, primarily strokes and myocardial infarctions[3].

MATERIALS AND METHODS:

Materials:

The Diltiazem Hydrochloride was obtained as a gift sample from splendid laboratories, Pune. Gum Kondagogu, Gum Olibanum and Locust Bean Gum were obtained from Girijan Co-operative corp. Ltd, Hyderabad. Sodium bicarbonate, Citric acid, PVP-K30 was gifted from MSN Labs Ltd, Hyderabad. All other chemicals used were of analytical grade.

Methods:

Wet Granulation Method [4]

Gastroretentive floating tablets of Diltiazem Hydrochloride were developed using the wet granulation method, incorporating varying amounts of Gum Konduga, Gum Olibanum, and Locust Bean Gum. All excipients were first passed through a #85 mesh sieve to ensure uniform particle size and thoroughly mixed. Granulation was performed using a binder solution consisting of 5% PVP K30 in isopropyl alcohol. Then passed through a #12 mesh sieve and dried at 45°C for 2 hours. After drying, the granules were resized using a #18 mesh sieve. The final blend was compressed into tablets using an 8 mm flat-faced punch on a Cadmach tablet press (Ahmedabad, India).

Table 1: Formulation trials of floating tablets of Diltiazem using Locust bean gum

Ingredients (mg)	DF1	DF2	DF3	DF4	DF5	DF6	DF7	DF8
Drug	80	80	80	80	80	80	80	80
Locust bean gum	30	40	50	60	30	40	50	60
Sodium Bicarbonate	30	30	30	30	45	45	45	45
Citric acid	10	10	10	10	10	10	10	10
MCC	80	70	60	50	65	55	45	35
PVP K-30	10	10	10	10	10	10	10	10
Mg stearate	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5
Total weight	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**

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Table 2: Formulation trials of floating tablets of Diltiazem using Gum Kondagogu

Ingredients (mg)	DF9	DF10	DF11	DF12	DF13	DF14	DF15	DF16
Drug	80	80	80	80	80	80	80	80
Gum Kondagogu	50	60	70	80	50	60	70	80
Sodium Bicarbonate	30	30	30	30	45	45	45	45
Citric acid	10	10	10	10	10	10	10	10
MCC	60	50	40	30	45	35	25	15
PVP K-30	10	10	10	10	10	10	10	10
Mg stearate	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5
Total weight	250	250	250	250	250	250	250	250

Table 3: Formulation trials of floating tablets of Diltiazem using Locust bean gum

Ingredients (mg)	DF17	DF18	DF19	DF20	DF21	DF22	DF23	DF24
Drug	80	80	80	80	80	80	80	80
Gum Olibanum	55	65	75	85	55	65	75	85
Sodium Bicarbonate	30	30	30	30	45	45	45	45
Citric acid	10	10	10	10	10	10	10	10
MCC	55	45	35	25	40	33	29	10
PVP K-30	10	10	10	10	10	10	10	10
Mg stearate	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5
Total weight	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**

Evaluation Parameters

Precompression parameters [5,6]

Before the compression process, the formulation powder blends were assessed for their bulk and tapped density, from which the compressibility index and Hausner's ratio were derived. Additionally, the flow properties of the powder blend were evaluated using the angle of repose.

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Evaluation of Floating Tablets [7,8]

Post compression parameters: The prepared tablets were evaluated for quality control tests like weight variation, hardness, thickness, friability and content uniformity.

Weight variation: Ten tablets were selected randomly from each batch and weighed individually, calculating the average weight and comparing the individual tablet weight to the average. From this; percentage weight difference was calculated and then checked for USP

specifications.

Hardness and friability: The Hardness (or) Crushing Strength(or)Tensile Strength of prepared tablets is said to be load required for cleft a tablet into tiny fragments when placed on edge of the hardness tester and its unit is Kg/cm^2. The sample size of the present parameter is 3 from each batch of the formulation.

Whereas friability of all batch formulations was predicted with aid of ROCHE FRIABILATOR (Make: Electro lab, India) and computed using below formula;

$$\%\ Friability = \frac{W1 - W2}{W2} * 100$$

Where;

W1= Mass of tablet before friability; W2=Mass of the tablet after friability

***In vitro* buoyancy studies:** The *in vitro* buoyancy of the tablets was evaluated by measuring the floating lag time. Each tablet was placed in a 100 mL beaker containing 0.1N hydrochloric acid, and the time taken for the tablet to ascend and begin floating on the surface was recorded as the floating lag time. The duration for which the tablet remained buoyant without sinking was noted as the total floating time.[10].

***In vitro* Dissolution Studies[11]:**

Dissolution Apparatus	:	USP Dissolution Apparatus Type II (Paddle)
Dissolution Medium	:	0.1NHydrochloricAcid (pH1.2)
Dissolution Medium Volume	:	900ml
Temperature	:	37±0.2°C
Aliquot Volume	:	5ml
ReplishingVolume	:	5ml
Speed	:	100rpm
Estimation	:	237 nm&290inUV Spectrophotometer
Time Intervals (Hours)	:	1,2,3,4,6,8,10&12

Stability studies: Stability studies were performed in accordance with ICH guidelines by storing the formulations at $40 \pm 2°C$ and $75 \pm 5\%$ relative humidity for a period of three months using a stability chamber (Thermo Lab, Mumbai). Samples were collected at specified time intervals—0, 30, 90, and 180 days—for evaluation. Key in vitro parameters such as drug content, floating lag time, and stability[12].

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RESULTS AND DISCUSSION

In the current study, Diltiazem Hydrochloride, which is employed in antihypertensive therapy, has been applied as an active pharmaceutical ingredient and is regarded as a strong candidate for minimizing dosing frequency, particularly in solid oral sustained release formulations, and enhancing compliance in ulcer treatment. This formulation is presented in the form of gastroretentive floating tablets designed to ensure the desired sustained and thorough release over an extended time frame.

Precompression Parameters

The results of precompression evaluation parameters are shown in (Table 4). All the pre-compression evaluation parameters were within the USP Pharmacopoeia limits.

Post- compression Parameters

The outcomes of the post-compression evaluation parameters are presented in (Table 5). The weight variation across all formulations was found to be within the permissible limit of ± 5% of the total tablet weight. The appropriate hardness of compressed tablets is regarded as a crucial factor for the end user. The measured crushing strength of the manufactured tablets from formulations F1-F24 ranged from 4.0 to 5.0 kg/cm2. The thickness of all formulations varied between 4.1 and 4.5 mm. The friability of all prepared formulations was between 0.53% and 0.79%, with the acceptable friability limits being between 0% and 1%. The drug content for all formulations ranged from 94.23% to 99.68%, and this content is influenced by the angle of repose, as it reflects the uniform flow characteristics of the powder blend, which facilitates even distribution of the drug across all formulations and ensures content uniformity in all batches. Tablets from all batches exhibited a floating lag time of less than 60 seconds, irrespective of the viscosity and polymer content, due to the generation of CO2 from the reaction between sodium bicarbonate and the dissolution medium. The entrapment of gas within the hydrated polymeric matrices allows the dosage form to float by reducing the density of the matrices. The total floating time for the formulations using natural polymers exceeded 12 hours.

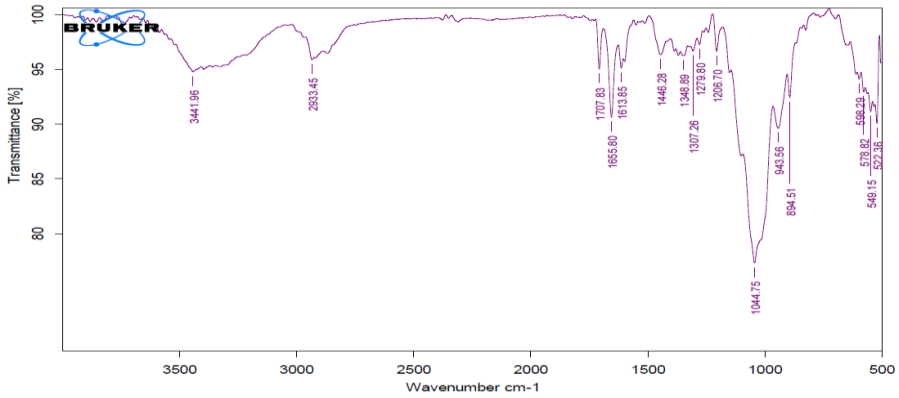

Figure 1: FTIR Spectrum of Pure Drug Diltiazem Hydrochloride

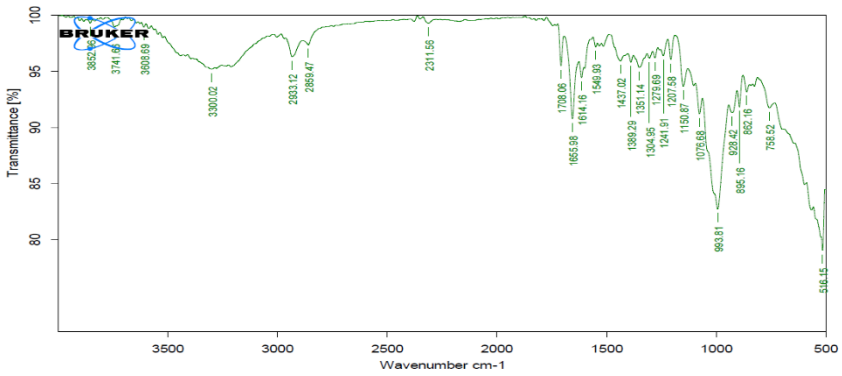

Figure 2. FTIR Spectrum of Pure Diltiazem Hydrochloride and Locust Bean Gum

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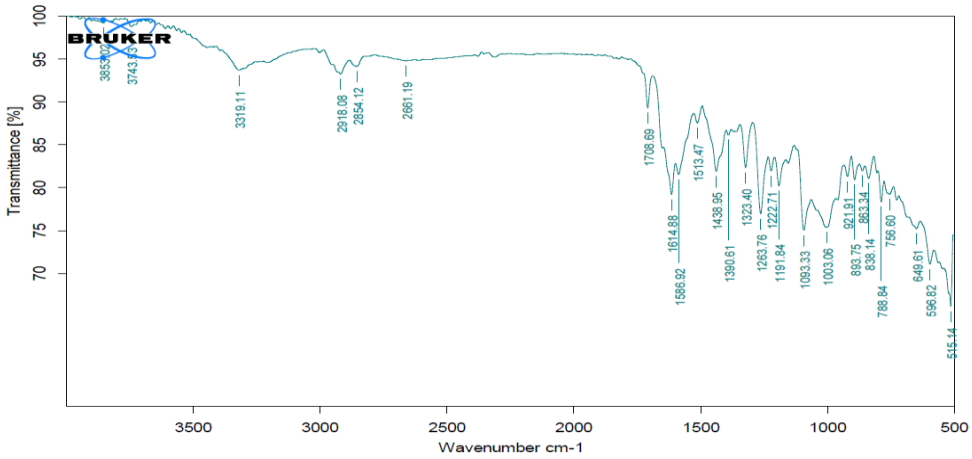

Figure 3. FTIR Spectrum of Pure Diltiazem Hydrochloride and Gum Kondagogu

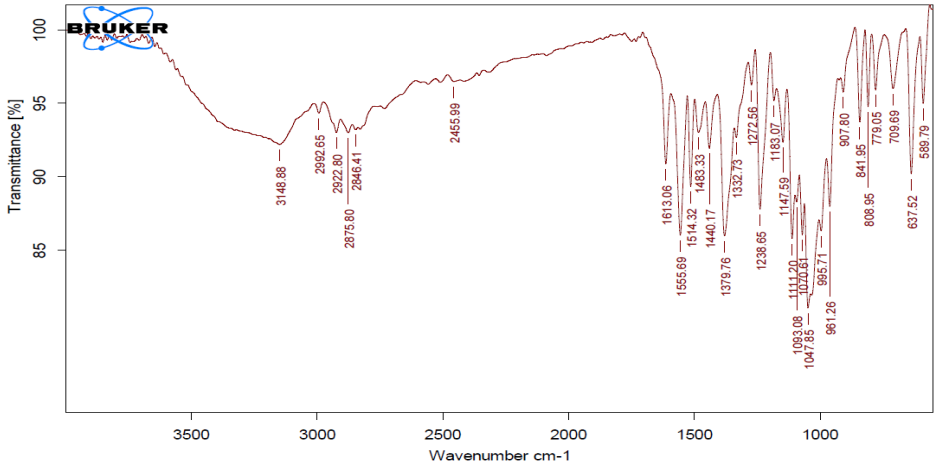

Figure 4. FTIR Spectrum of Pure Diltiazem Hydrochloride and Gum Olibanum

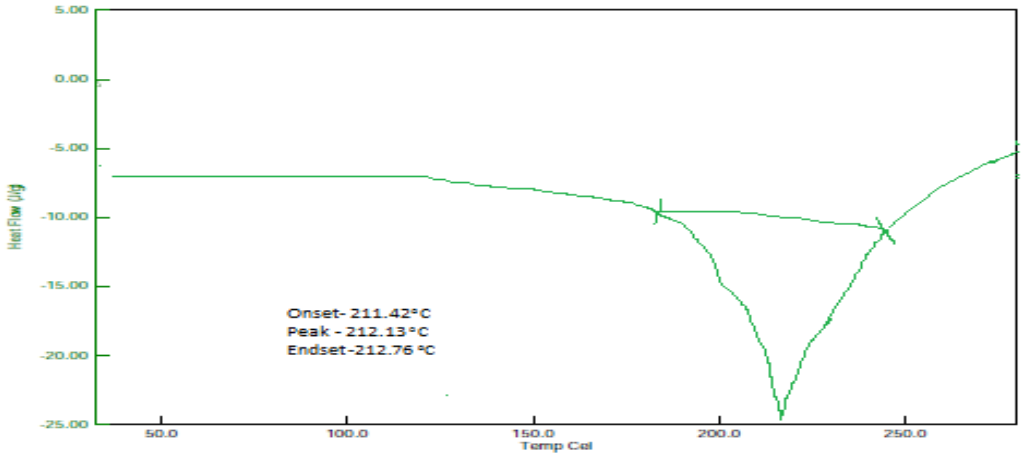

Figure 5: DSC of Pure Drug Diltiazem Hydrocloride

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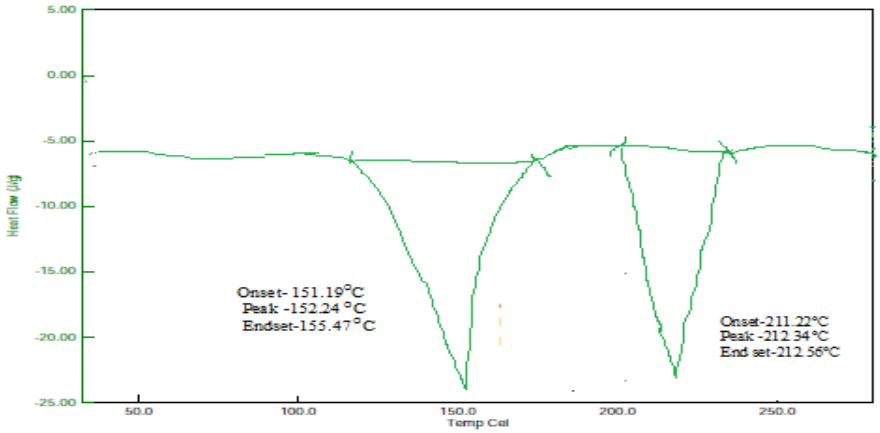

Figure 6: DSC of Pure Diltiazem Hydrochloride and Locust Bean Gum

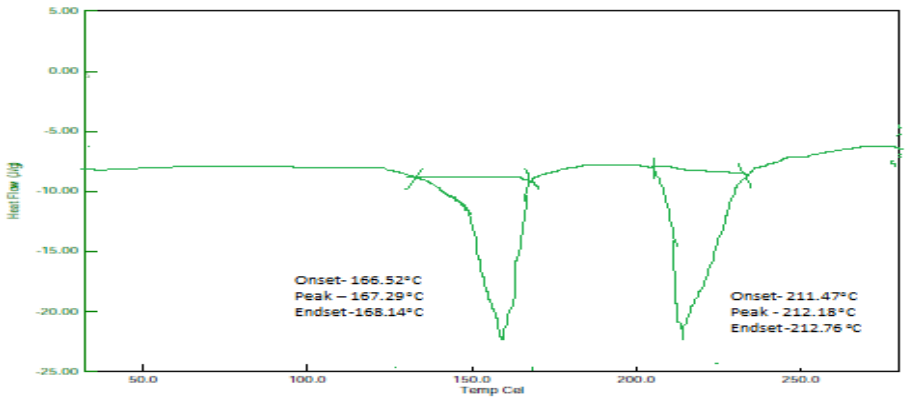

Figure 7: DSC of Pure Diltiazem Hydrochloride and Gum Kondagogu

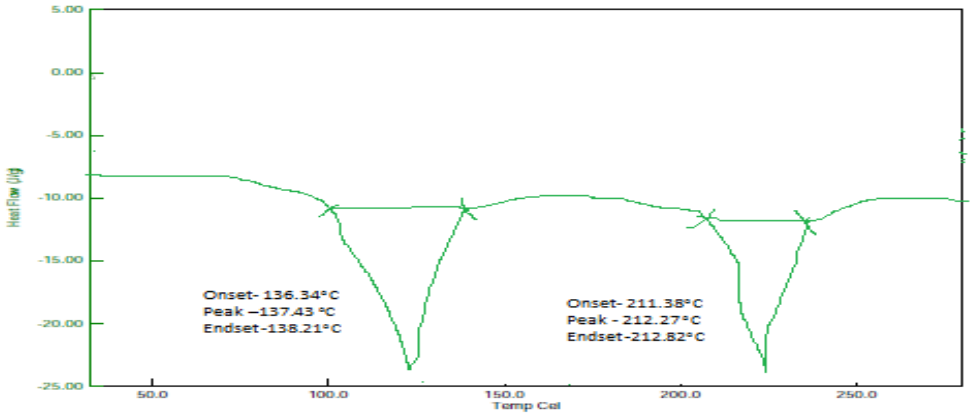

Figure 8: DSC of Pure Diltiazem Hydrochloride and Gum Olibanum

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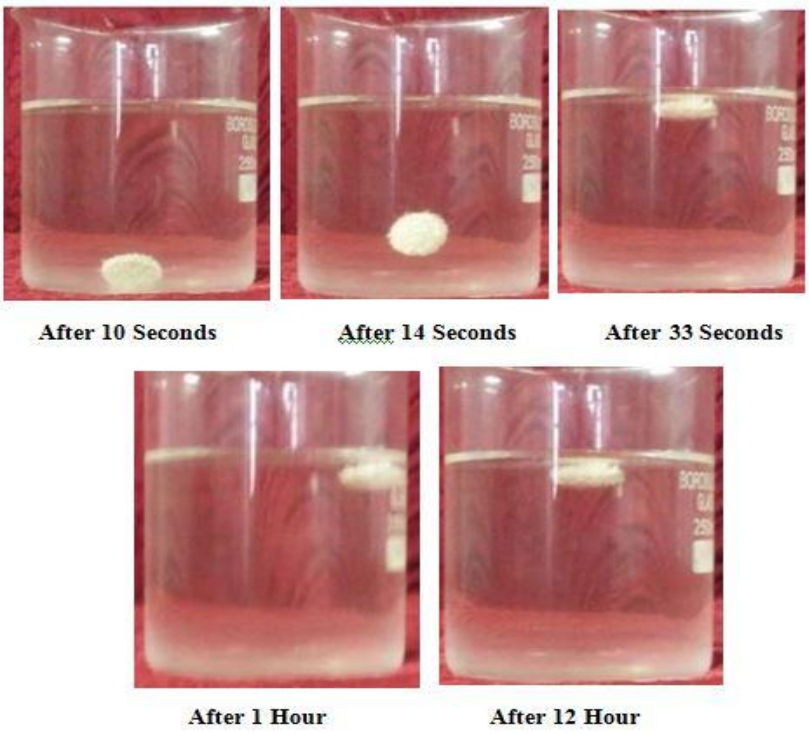

Figure 9: Floating lag time and Total floating time of Diltiazem Floating Tablets

Table 4: Physical properties of prepared powder blends of Floating tablet

Formulation	Bulk density (g/cc)	Tapped density (g/cc)	Angle of repose(Θ)	Carr's index (%)	Hausner ratio
DF1	0.56±0.02	0.59±0.01	23.34±0.4	10.28±0.8	1.12±0.02
DF2	0.57±0.12	0.59±0.04	24.67±0.3	10.29±1.0	1.13±0.07
DF3	0.58±0.04	0.65±0.05	25.54±0.1	10.15±0.7	1.12±0.09
DF4	0.51±0.04	0.67±0.04	24.89±0.2	11.37±0.6	1.13±0.03
DF5	0.66±0.02	0.69±0.02	22.56±0.1	11.24±0.8	1.12±0.05
DF6	0.51±0.21	0.65±0.12	24.30±0.1	10.22±0.5	1.13±0.06
DF7	0.53±0.06	0.63±0.03	23.56±0.2	10.36±1.0	1.13±0.06
DF8	0.54±0.01	0.67±0.03	23.67±0.3	10.13±0.8	1.11±0.03
DF9	0.58±0.01	0.62±0.01	24.56±0.3	10.46±0.7	1.14±0.02
DF10	0.57±0.13	0.68±0.06	23.66±0.2	11.49±0.5	1.12±0.01
DF11	0.54±0.09	0.66±0.12	24.34±0.2	10.25±0.5	1.14±0.01
DF12	0.58±0.06	0.65±0.21	23.99±0.5	11.36±0.5	1.11±0.01
DF13	0.55±0.01	0.68±0.04	24.14±0.3	10.68±0.4	1.13±0.02

DF14	**0.51±0.09**	**0.65±0.07**	**21.09±0.2**	**09.29±0.4**	**1.10±0.09**
DF15	0.54±0.01	0.64±0.04	23.78±0.4	10.43±0.3	1.11±0.03
DF16	0.55±0.02	0.62±0.07	23.45±0.4	10.63±0.2	1.12±0.06
DF17	0.58±0.21	0.67±0.03	24.09±0.3	11.48±0.8	1.13±0.09
DF18	0.57±0.03	0.66±0.08	24.05±0.2	11.92±0.3	1.13±0.02
DF19	0.55±0.02	0.62±0.12	24.06±0.2	11.44±0.6	1.15±0.08
DF20	0.58±0.06	0.65±0.1	25.78±0.1	10.13±0.5	1.12±0.05
DF21	0.58±0.07	0.64±0.03	24.34±0.4	11.12±0.4	1.15±0.02
DF22	0.57±0.15	0.65±0.04	25.12±0.3	10.39±0.2	1.13±0.03
DF23	0.59±0.13	0.67±0.13	25.45±0.3	10.64±0.4	1.12±0.02
DF24	0.57±0.12	0.66±0.05	24.56±0.2	09.64±0.6	1.13±0.07

Table 5: Physicochemical parameters of Diltiazem floating tablets

F. No	*Weight variation (mg)	#Thickness (mm)	#Hardness (Kg/Cm^2)	#Friability (%)	#Content uniformity (%)	Floating lag time (sec)	Total floating time (hrs)
DF1	248.65±1.2	4.3±0.12	4.4±0.12	0.56±0.01	96.23±0.63	56	>12
DF2	252.69±0.8	4.4±0.06	4.3±0.06	0.57±0.02	98.04±0.06	53	>12
DF3	247.04±0.5	4.2±0.06	4.2±0.06	0.64±0.03	96.56±0.14	51	>12
DF4	251.05±0.0	4.3±0.12	5.1±0.12	0.73±0.01	97.11±1.01	46	>12
DF5	250.54±0.4	4.4±0.00	4.4±0.00	0.64±0.02	95.23±1.08	45	>12
DF6	252.78±0.4	4.2±0.10	5.0±0.06	0.67±0.01	96.45±0.31	43	>12
DF7	251.65±0.3	4.3±0.10	4.4±0.10	0.54±0.02	97.91±0.49	41	>12
DF8	248.57±0.2	4.2±0.25	5.1±0.40	0.68±0.01	98.23±0.51	58	>12
DF9	251.76±0.3	4.4±0.06	5.1±0.06	0.59±0.00	97.13±0.56	56	>12
DF10	247.49±0.2	4.3±0.20	4.3±0.42	0.78±0.02	96.23±0.24	53	>12
DF11	250.53±0.4	4.3±0.06	5.0±0.06	0.77±0.01	98.97±0.21	48	>12
DF12	251.58±0.3	4.3±0.00	4.5±0.06	0.75±0.02	97.45±0.76	47	>12
DF13	252.34±0.2	4.2±0.26	4.7±0.35	0.723±0.02	98.45±0.48	42	>12
DF14	**250.99±0.5**	**4.1±0.21**	**5.4±0.33**	**0.54±0.03**	**99.68±0.23**	**33**	**>12**
DF15	248.65±0.2	4.3±0.06	5.1±0.23	0.66±0.02	97.45±0.36	59	>12
DF16	251.65±0.3	4.3±0.25	4.6±0.23	0.67±0.01	98.45±0.69	55	>12
DF17	252.79±0.4	4.4±0.15	5.2±0.32	0.58±0.01	97.34±0.35	54	>12
DF18	250.87±0.1	4.3±0.25	4.5±0.35	0.67±0.01	98.56±0.23	51	>12
DF19	248.65±0.2	4.3±0.06	4.1±0.23	0.76±0.02	97.45±0.36	48	>12
DF20	247.32±0.2	4.3±0.12	5.2±0.20	0.64±0.03	96.18±0.81	46	>12
DF21	251.16±0.8	4.1±0.10	4.3±0.81	0.53±0.89	97.23±0.13	52	>12
DF22	252.33±0.2	4.2±0.15	5.0±0.25	0.62±0.23	96.59±0.65	49	>12
DF23	248.58±0.7	4.2±0.33	4.7±0.12	0.59±0.55	98.38±0.33	53	>12
DF24	251.11±0.4	4.4±0.28	4.3±0.45	0.72±0.67	97.42±0.27	48	>12

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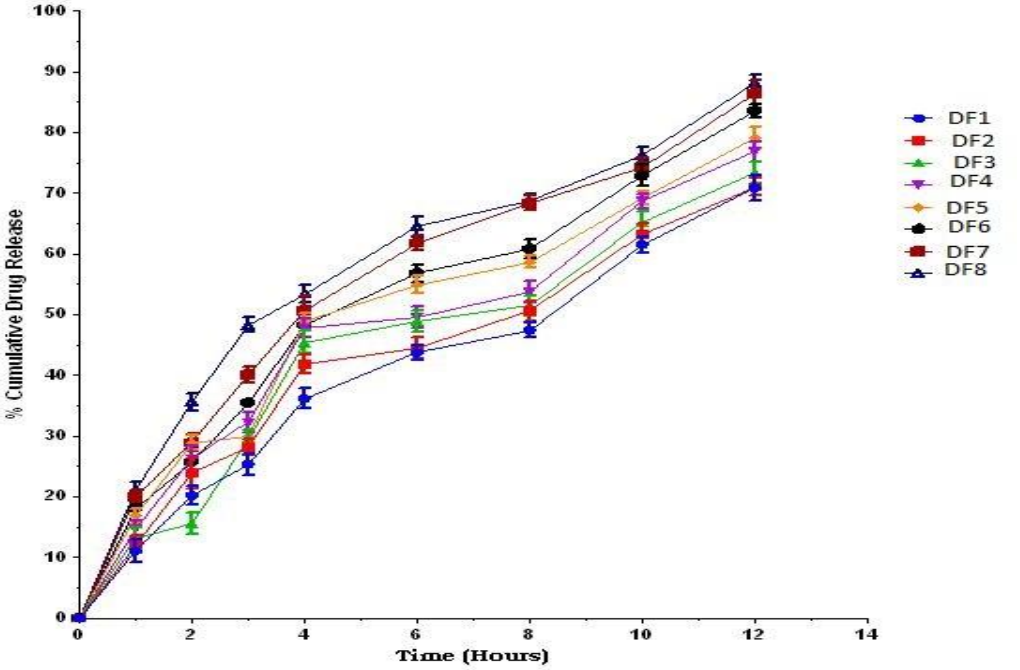

Figure 9: Comparison of *in vitro* Percentage drug release of Diltiazem floating tablet formulations DF1-DF8

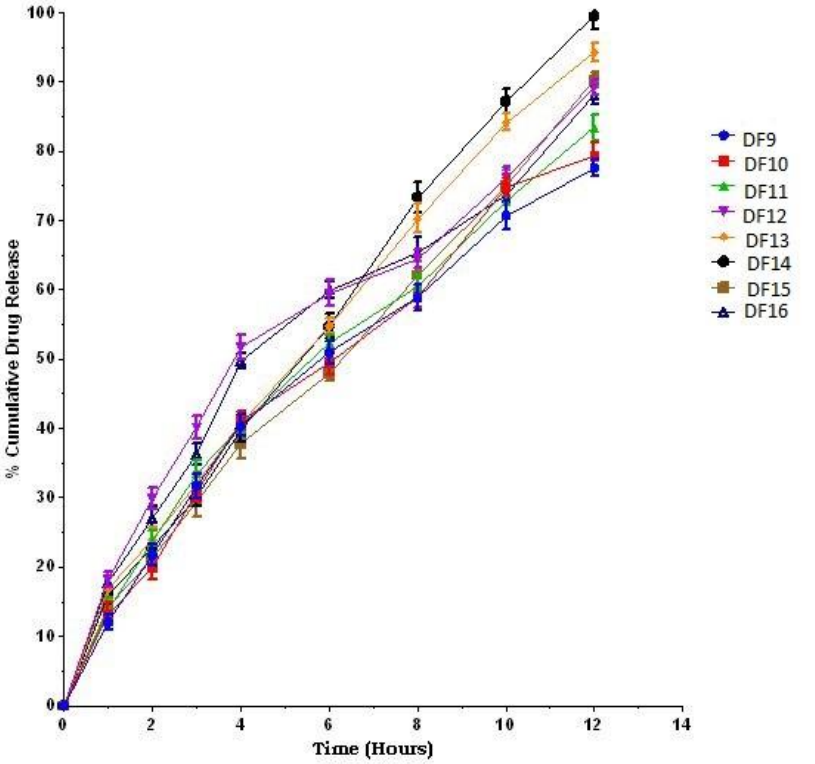

Figure 10: Comparison of *in vitro* Percentage drug release of Diltiazem floating tablet formulations LF9-LF16

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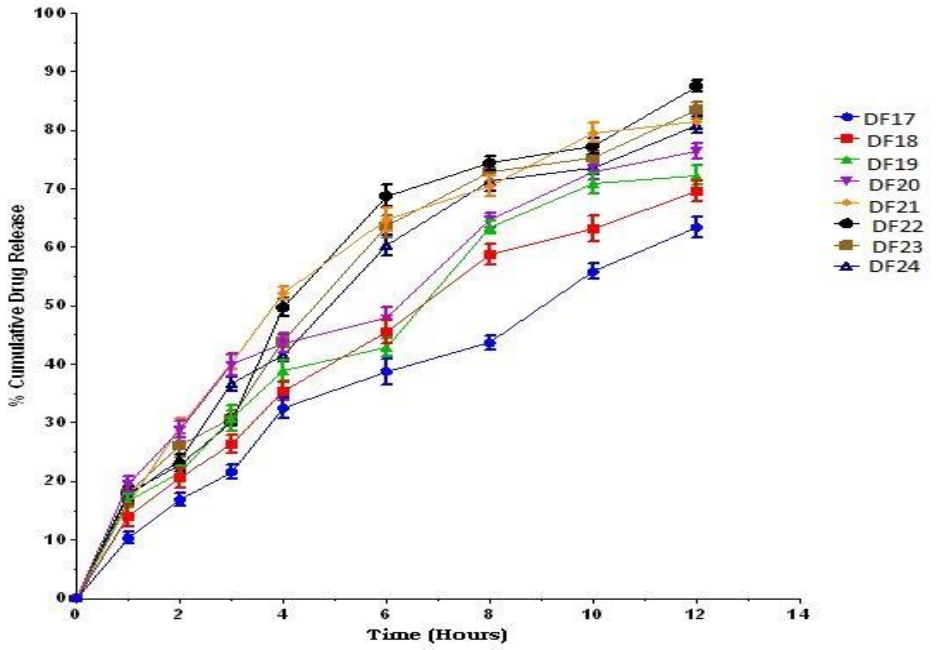

Figure 11: Comparison of *in vitro* Percentage drug release of Diltiazem floating tablet formulations LF17-LF24

From the above figures (**Figure 9, 10 and 11**) it can be observed that the polymerGum Kondagogu has sustaining effect on the release of drug from the floatingmatrix tabletof A comparative study was conducted on Diltiazem Hydrochloride using Locust Bean Gum and Gum Olibanum as natural polymers. Variations in drug release profiles were observed across different formulations, primarily due to differing concentrations of these polymers. The polymer levels were incrementally increased to evaluate their effectiveness in controlling drug release. Among all formulations tested, **Formulation DF14** demonstrated optimal performance. It exhibited excellent buoyancy characteristics and was capable of sustaining drug release for up to **12 hours**. The drug release from these formulations was primarily governed by a **diffusion-controlled mechanism**, as evidenced by high correlation coefficients with the **Higuchi and Korsmeyer-Peppas models**.

Mathematical treatment of optimized formula of Diltiazem Hydrochloride floating tablets

In vitro dissolution testing plays a crucial role in drug development, especially for assessing bioequivalence. Several models exist to describe drug dissolution profiles, where the amount of drug dissolved is a function of time and is related to the dosage form. To quantitatively analyze the data from dissolution tests, a generic equation is often employed to mathematically interpret the dissolution curve, taking into account parameters specific to the formulation.

For water-soluble drugs incorporated into a matrix, release typically occurs via diffusion. In contrast, for poorly water-soluble drugs, the matrix's self-erosion becomes the primary mechanism for release. By comparing experimental release data to established mathematical models, the dissolution process can be better understood and quantitatively described.

Table 6: Parameters after Accelerated Stability Study of Optimized Formulation DF14

Parameters	**Temperature Maintained at 40±2^{0}C; relative humidity (RH) maintained at 75%±5%RH**			
	Initial	**After 1 month**	**After 3 months**	**After 6 months**
Drug content (%)	99.68±0.24	98.96±0.69	98.13±0.38	98.12±0.23
***In vitro* drug release (%)**	99.54±1.28	99.10±1.56	98.82±1.43	98.50±1.38
Floating lag time	33	33	34	35

No alterations were noted in the percentage of drug content, in vitro drug release assessments, and floating lag time throughout the storage of the optimized formulation, with the findings summarized in Table 6. Therefore, the optimized formulation was determined to be stable.

CONCLUSION

In the current study, it can be inferred that the floating tablets of Diltiazem present an innovative and promising strategy for administering Diltiazem in the treatment of gastric ulcers. The optimised formulation DF14 incorporates Gum Kondagagu along with a gas-generating agent. When comparing the in-vitro clemency profile of Diltiazem with that of the marketed product, the optimised formulation DF14 exhibited a drug clemency of 99.54±1.26% within 12 hours, while the marketed product also released 99.54% of the API in the same timeframe. The predominant mechanism of drug release is characterised by zero array kinetics and non-Fickian transport, achieved through a combination of diffusion and erosion. This indicates that both water diffusion and polymer rearrangement play a crucial role in the drug clemency process. The clemency rate constant for the optimised formulation DF14 was sufficiently low, extending the drug delivery duration. These findings are promising, as an increased gastric abode time is a critical factor for boosting the bioavailability of drugs incorporated in prolonged or sustained clemency dosage forms.

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