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Formulation and Evaluation of Floating Drug Delivery System for the Treatment of H. Pylori Using Carvacrol

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H. pylori, Carvacrol, floating drug delivery system, FDDS

ABSTRACT:

Helicobacter pylori (H. pylori) infection is a prevalent and challenging condition often associated with peptic ulcers and gastric malignancies. Traditional antibiotic treatments face limitations due to antibiotic resistance and suboptimal drug delivery to the gastric mucosa. This study aims to formulate and evaluate a floating drug delivery system (FDDS) incorporating carvacrol, a potent antimicrobial agent with activity against H. pylori, to enhance localized drug action in the stomach. The FDDS was developed using an effervescent approach, incorporating gas-generating agents and hydrocolloids to achieve buoyancy. Carvacrol was selected for its broad-spectrum antimicrobial properties and ability to disrupt H. pylori biofilms. The formulation was optimized through a series of pre-formulation studies to determine the ideal polymer concentrations and ratios, ensuring optimal floatation and sustained drug release.

Characterization of the FDDS involved evaluating its buoyancy, drug release profile, and antimicrobial efficacy. In vitro buoyancy tests demonstrated that the optimized formulation remained buoyant for over 12 hours, providing prolonged gastric retention. Drug release studies using simulated gastric fluid indicated a sustained release of carvacrol over 8 hours, aligning with therapeutic needs for H. pylori eradication. Antimicrobial testing against H. pylori strains confirmed the formulation's efficacy, showing significant inhibition of bacterial growth and biofilm formation. The developed FDDS exhibited excellent potential for targeted therapy against H. pylori, offering prolonged drug residence time in the stomach and sustained antimicrobial action. These findings suggest that carvacrol-based floating drug delivery systems could represent a promising alternative to conventional H. pylori treatments, potentially improving patient outcomes and reducing the prevalence of antibiotic resistance. Further in vivo studies and clinical trials are warranted to confirm these promising results and assess the long-term benefits and safety of this novel therapeutic approach.

Introduction

In the realm of pharmaceutical sciences, the development of efficient drug delivery systems is paramount to enhancing therapeutic efficacy and patient compliance. Among the innovative approaches, Gastric Floating Drug Delivery Systems (GFDDS) have garnered significant attention. [1] GFDDS are designed to prolong the gastric residence time of drugs, ensuring a sustained release in the stomach. This strategy is particularly beneficial for medications that are absorbed

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primarily in the stomach or the upper part of the small intestine, or those that act locally in the stomach.

The fundamental principle behind GFDDS is buoyancy. These systems are formulated to have a lower density than gastric fluids, allowing them to float on the stomach's surface and remain in the gastric region for an extended period. This floating capability ensures that the drug is released gradually, maintaining a consistent drug concentration in the blood and enhancing bioavailability.[2-3]

Several techniques are employed in creating GFDDS, including effervescent systems, non-effervescent systems, and bioadhesive systems. Effervescent systems generate carbon dioxide when in contact with gastric fluids, aiding buoyancy. Non-effervescent systems rely on gel-forming polymers that swell upon hydration to achieve floatation. Bioadhesive systems, on the other hand, adhere to the gastric mucosa, ensuring the drug remains in the stomach.[4]

The advantages of GFDDS are multifaceted. They can improve the bioavailability of drugs with narrow absorption windows, reduce the frequency of dosing, minimize fluctuations in plasma drug concentrations, and improve patient compliance. Moreover, GFDDS can be particularly advantageous for treating conditions such as peptic ulcers, gastroesophageal reflux disease (GERD), and chronic gastritis, where localized drug action in the stomach is desirable.[5]

However, the development of GFDDS also presents challenges. Formulating a system with the optimal balance of buoyancy and drug release rate requires meticulous design. Factors such as the density of the formulation, the rate of hydration and swelling of polymers, and the gastric motility patterns must be carefully considered.[6-8]

In summary, Gastric Floating Drug Delivery Systems represent a promising and innovative approach to oral drug delivery. By ensuring prolonged gastric retention and sustained drug release, GFDDS can significantly enhance the therapeutic outcomes of various medications, offering a strategic advantage in the treatment of several gastrointestinal and systemic conditions.[9,16]

1. Materials and methods

Materials:

Carvacrol

Polymers (e.g., Hydroxypropyl methylcellulose (HPMC), Eudragit)

Gas-generating agents (e.g., Sodium bicarbonate, citric acid)

Other excipients (e.g., lactose, magnesium stearate)

Preparation of Floating Tablets of Carvacrol Using the Direct Compression Method [10]

Materials Carvacrol

Polymers: Hydroxypropyl methylcellulose (HPMC) – for controlled release

Eudragit – for additional sustained release properties

Gas-generating agents: Sodium bicarbonate – to produce gas and impart buoyancy

Citric acid – to react with sodium bicarbonate

Fillers: Lactose – for tablet mass

Binders: Polyvinylpyrrolidone (PVP) – to ensure tablet cohesion

Preformulation Studies [11-12]

Compatibility studies of Carvacrol and HPMC

Carvacrol and HPMC compatibility studies utilizing FTIR (Fourier-transform infrared spectroscopy) and DSC (differential scanning calorimetry) could be conducted to understand the interaction between these two substances. Here's a general outline of how such studies might be conducted:

Sample Preparation: Prepare samples containing different ratios of Carvacrol and HPMC. Ensure that the samples cover a wide range of concentrations to observe any potential interactions comprehensively.

FTIR Analysis:

Perform FTIR analysis on individual samples of Carvacrol and HPMC to obtain their respective spectra. This establishes baseline spectra for each substance.

Then, prepare samples containing mixtures of Carvacrol and HPMC in varying ratios.

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Analyze these mixtures using FTIR to observe any shifts, peaks, or changes in the spectra compared to the individual spectra of Carvacrol and HPMC. These changes could indicate interactions between the two substances, such as hydrogen bonding or chemical reactions.

DSC Analysis:

Conduct DSC analysis on individual samples of Carvacrol and HPMC to determine their thermal behavior, such as melting points, glass transition temperatures, and heat capacities.

Prepare mixtures of Carvacrol and HPMC in different ratios and analyze them using DSC.

Compare the DSC curves of the mixtures with those of the individual components to identify any changes in the thermal properties of the mixtures. This can provide insights into possible interactions between Carvacrol and HPMC, such as compatibility or phase separation.[15]

Data Interpretation:

Analyze the FTIR spectra for any new peaks, shifts, or changes in peak intensity, which could indicate chemical interactions or complex formation between Carvacrol and HPMC. Interpret the DSC data for any alterations in thermal behavior, such as changes in melting points or enthalpy, which could suggest compatibility or incompatibility between Carvacrol and HPMC. Correlate the results from FTIR and DSC to draw conclusions about the compatibility of Carvacrol and HPMC and to understand the nature of any interactions between them.

Based on the FTIR and DSC data analysis, draw conclusions regarding the compatibility of Carvacrol and HPMC. Determine whether they can be used together in formulations without any adverse interactions or if certain conditions need to be met to ensure compatibility. Provide recommendations for further studies or adjustments in formulation if needed based on the findings. This process can provide valuable insights into the compatibility of Carvacrol and HPMC and guide formulation efforts for pharmaceutical or other applications.

Lubricants: Magnesium stearate – to prevent sticking during tablet formation.

Table no. 01: Formulation of F1-F7

Formulation code	Drug %	HPMC K4M (%)	HPMC K15M (%)	NaHCO3 (%)	Mg stearate (%)	Talc (%)
F1	62.5	23	11.50	11.50	0.5	1
F2	62.5	11.50	11.50	13.00	0.5	1
F3	62.5	23	00	11.50	0.5	1
F4	62.5	00	23	11.50	0.5	1
F5	62.5	13	13	10	0.5	1
F6	62.5	00	23	10	0.5	1
F7	62.5	3	23	10	0.5	1

Methodology [13-14]

Weighing:

Accurately weigh all ingredients according to the formulation requirements. For example, for a batch of 100 tablets, if each tablet should contain 50 mg of carvacrol, the total amount needed would be 5 g of carvacrol.

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Mixing:

Primary Mixing: Mix carvacrol, HPMC and other ingredients thoroughly in a mortar or a high-shear mixer for 10-15 minutes to ensure uniform distribution.

Secondary Mixing: Add sodium bicarbonate to the primary mix and blend for another 5-10 minutes. Ensure these agents are evenly distributed to guarantee consistent gas generation for floating.

Final Mixing: Add magnesium stearate to the blend and mix gently for an additional 2-3 minutes to avoid over-lubrication, which can affect tablet hardness and dissolution.

Compression:

Use a tablet press equipped with appropriate punch and die sets to compress the mixed powder into tablets. Set the tablet press parameters (compression force, tablet size, and thickness) based on preliminary trials to achieve the desired tablet properties (e.g., hardness, weight, and dimensions).

Characterization:

1. **Weight Variation**:

The weight variation test ensures that each tablet in a batch contains a uniform amount of the active ingredient and meets pharmacopeia standards. This consistency is crucial for the efficacy, safety, and quality of the pharmaceutical product.

Materials

Analytical balance with precision of 0.001 g 20 randomly selected tablets from the batch

Procedure

Selection of Tablets:

Randomly select 20 tablets from the batch for the weight variation test. Ensure the selection is truly random to get a representative sample of the batch.

Weighing:

Individually weigh each of the 20 tablets using an analytical balance. Record the weight of each tablet accurately.

Calculation of Average Weight:

Calculate the average weight of the 20 tablets using the formula:

Average weight = ∑ weight of individual tablets/20

Comparison with Pharmacopeia Standards:

Compare the individual weights of the tablets to the average weight. The acceptable weight variation depends on the average weight of the tablets and follows pharmacopeia guidelines, typically:

For tablets weighing less than 80 mg: ±10% deviation allowed

For tablets weighing 80 mg to 250 mg: ±7.5% deviation allowed

For tablets weighing more than 250 mg: ±5% deviation allowed

Determination of Compliance:

Determine if the individual weights fall within the acceptable range:

Acceptable range =Average weight±(Average weight×allowed deviation)

Acceptable range=Average weight±(Average weight×allowed deviation)

2. **Hardness:** The hardness test assesses the mechanical strength of the tablets to withstand handling, packaging, and transportation without breaking or crumbling. It also ensures that the tablets have sufficient strength to maintain their integrity during administration but can disintegrate appropriately in the gastric environment.

Materials

Tablet hardness tester (e.g., Monsanto hardness tester, Pfizer hardness tester, or digital hardness tester) 10 randomly selected tablets from the batch

Procedure

Selection of Tablets:

Randomly select 10 tablets from the batch for the hardness test. This ensures a representative sample of the batch.

Testing with Hardness Tester:

Monsanto Hardness Tester:

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Place the tablet between the anvils.

Turn the screw knob to apply a compressive force until the tablet breaks.

Read the hardness value directly from the scale.

Pfizer Hardness Tester:

Place the tablet between the jaws.

Press the handle to apply force until the tablet breaks.

Read the hardness value from the gauge.

Digital Hardness Tester:

Place the tablet on the testing platform.

Start the machine to apply a compressive force automatically until the tablet breaks.

Read the hardness value displayed on the screen.

Recording Results:

Record the hardness value (usually in kg/cm² or Newtons) for each of the 10 tablets.

Calculating Average Hardness:

Calculate the average hardness of the 10 tablets using the formula:

Average hardness = ∑ hardness of individual tablets / 10

3. **Friability**:

The friability test assesses the durability of the tablets to withstand abrasion during handling, packaging, and transportation. It measures the tendency of tablets to crumble or break when subjected to mechanical stress.

Materials

Friabilator (e.g., Roche friabilator)

Analytical balance with precision of 0.001 g 20 randomly selected tablets from the batch

Procedure

Selection of Tablets:

Randomly select 20 tablets from the batch for the friability test.

Initial Weighing:

Dust off any loose particles from the tablets using a soft brush.

Accurately weigh the 20 tablets together and record the initial weight (W_i).

Friabilator Testing:

Place the weighed tablets into the friabilator drum. Set the friabilator to rotate at 25 rpm for 4 minutes, or 100 revolutions. After the rotation, remove the tablets from the friabilator.

Final Weighing:

Remove dust from the tablets again using a soft brush. Weigh the tablets together and record the final weight (Wf).

The tablets pass the friability test if the percentage friability is ≤ 1.0%. Tablets that lose more than 1.0% of their weight are considered too friable.

4. **Thickness**: The thickness test measures the physical dimensions of the tablets to ensure uniformity in size, which is crucial for consistency in tablet production, packaging, and consumer acceptance. It also affects the overall appearance and uniformity of the dosage form.

Materials

Vernier caliper or thickness gauge

10 randomly selected tablets from the batch

Procedure

Selection of Tablets:

Randomly select 10 tablets from the batch for the thickness test. This ensures a representative sample of the batch.

Measurement:

Using a vernier caliper or thickness gauge, measure the thickness of each tablet. Ensure the device is calibrated correctly before use.

Place the tablet between the jaws of the caliper or on the platform of the thickness gauge.

Close the jaws or activate the gauge to measure the thickness of the tablet.

Record the thickness of each tablet in millimeters (mm).

Calculation of Average Thickness:

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Calculate the average thickness of the 10 tablets using the formula:

Average thickness=∑thickness of individual tablets10Average thickness=10∑thickness of individual tablets

Ensure that the thickness of the tablets is within the specified range for the product. The acceptable range is usually determined during the formulation development stage and specified in the product specifications.

The average thickness:

Ensure that the thickness values do not deviate significantly from the average value. The acceptable deviation range should be predefined based on formulation requirements, typically within ±5% of the average thickness.

Consistent tablet thickness is crucial for ensuring uniformity in tablet weight and drug content. Affects the dissolution rate and bioavailability of the drug. Ensures proper packaging and handling of the tablets.

Optimizing Thickness:

Adjust the compression force during tablet manufacturing if thickness variations are observed. Higher compression force can reduce thickness and increase hardness, while lower force can increase thickness and reduce hardness. Ensure uniform filling of the die cavity in the tablet press to maintain consistent tablet dimensions.

5. Floating Behaviour:

In Vitro Buoyancy Study: Place the tablets in a beaker containing 900 mL of simulated gastric fluid (SGF, pH 1.2) maintained at 37±0.5°C. Observe and record the floating lag time (time taken for the tablet to rise to the surface) and the total floating duration (time the tablet remains buoyant).

In Vitro Drug Release:

Use a USP dissolution apparatus (e.g., paddle method) to study the release profile of carvacrol from the tablets. Place the tablets in 900 mL of SGF at 37±0.5°C and rotate the paddle at 50 rpm. Collect samples at predetermined intervals (e.g., 1, 2, 4, 6, 8, 10, and 12 hours) and analyze the carvacrol content using a suitable analytical method (e.g., HPLC or UV spectrophotometry). Plot the cumulative percentage of drug released versus time and analyse the release kinetics.

The in vitro drug release study evaluates the rate and extent of carvacrol release from the floating tablets over a specified period. This test is crucial to ensure the drug is released in a controlled manner, allowing for prolonged therapeutic effect and enhanced efficacy against H. pylori.

Materials

USP Dissolution apparatus (e.g., Apparatus II - Paddle),Simulated gastric fluid (SGF, pH 1.2)

900 mL dissolution medium (SGF),Water bath maintained at 37±0.5°C,Sampling device (syringe with filter),Analytical method (e.g., UV-Vis spectrophotometer or HPLC),Floating tablets of carvacrol

Procedure

Preparation of Dissolution Medium:

Prepare 900 mL of simulated gastric fluid (SGF) with a pH of 1.2.

Setting Up the Apparatus:

Fill the dissolution vessels with 900 mL of SGF. Maintain the temperature of the dissolution medium at 37±0.5°C using a water bath. Place the paddle in the vessels and set the rotation speed to 50 rpm.

Placement of Tablets:

Place one floating tablet of carvacrol in each dissolution vessel.

Sampling:

At predetermined time intervals (e.g., 1, 2, 4, 6, 8, 10, and 12 hours), withdraw 5 mL of the dissolution medium using a syringe with a filter to remove any undissolved particles. Immediately replace the withdrawn volume with fresh SGF maintained at 37±0.5°C to maintain a constant volume.

Analysis:

Analyze the samples for carvacrol content using a suitable analytical method:

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UV-Vis Spectrophotometer: Measure the absorbance of the samples at the specific wavelength for carvacrol and calculate the concentration using a standard calibration curve. **HPLC**: Inject the samples into the HPLC system and determine the carvacrol concentration using a suitable detector and calibration curve.

Calculation of Cumulative Release:

Calculate the cumulative percentage of carvacrol released at each time point using the formula:

Cumulative percentage release = (Amount of carvacrol released at each time point / Total amount of carvacrol in the tablet) × 100

Plotting the Release Profile:

Plot the cumulative percentage release versus time to obtain the drug release profile.

Analyze the release profile to determine if the floating tablets provide a sustained release of carvacrol over the 12-hour period.

Significance:

Ensures the floating tablets release carvacrol in a controlled manner, maintaining effective drug levels in the gastric environment for prolonged periods. Helps in optimizing the formulation to achieve the desired release profile, ensuring therapeutic efficacy against H. pylori. If the release rate is too fast or too slow, adjustments can be made to the formulation (e.g., changing the polymer type or concentration, adjusting the compression force during tablet manufacture). The in vitro drug release study is essential to confirm that the floating tablets of carvacrol provide a sustained release profile, ensuring prolonged therapeutic action against H. pylori. Regular testing and optimization ensure that the tablets meet the desired release specifications and provide consistent efficacy.

3. Results and discussion

Construction of standard calibration curve of carvacrol in 90% ethanol the absorbance of the solution was measured at 276 nm, using uv spectrometer with 90% Ethanol as blank. The values are shown in table no. 02. A graph of absorbance vs concentration was plotted which indicated in compliance to beer's law in the concentration range 0 to 100 µg/ml.

Table no. 02: Standard Calibration curve of carvacrol

Conc. (ppm)	Absorbance
0	0.0000
20	0.8697
40	1.5649
60	2.3754
80	3.0986
100	3.8567

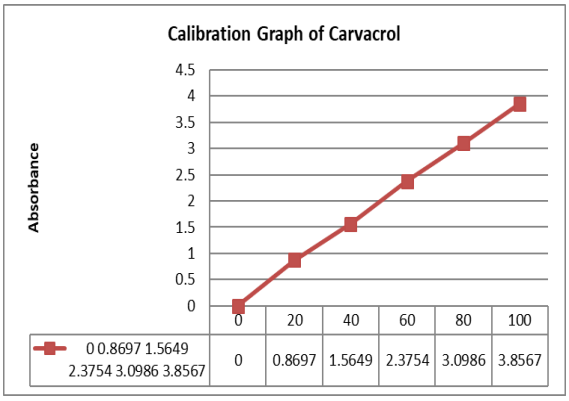

Fig. no. 01: Standard calibration curve of carvacrol

Table no. 03: Precompression studies of carvacrol floating tablets

Formulation Code	Bulk Density (kg/cm^3)	Tapped Density (kg/cm^3)	Cars Index	Hausners ratio	Angle of repose ()
F1	0.41	0.48	17.09	1.32	24.96
F2	0.42	0.46	16.75	1.40	25.04
F3	0.46	0.53	15.45	1.29	23.45

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F4	0.39	0.43	16.24	1.34	28.45
F5	0.38	0.45	17.02	1.39	24.96
F6	0.42	0.47	16.58	1.45	22.48
F7	0.39	0.43	13.28	1.37	24.28

The carvacrol floting tablets were evaluated for their flow properties; the results for the blends of compression tablets were shown in table no. 03. The bulk density and the tapped density for all formulations were found to be almost similar. The carr's index and hausner's ratio were found to be in the range of ≤18 and 1.0 to 1.23 respectively, indicating good flow and compressibility of the blends. The angle of repose for all the formulations was found to be in the range of 9.92-12.73˚ which indicating passable flow (i.e. Incorporation of glidant will enhance its flow).

Table no. 04: Post compression studies of carvacrol floating tablets

Formulation Code	%weight variation	Thickness (mm)	%friability	%drug content	Hardness (kg/cm2)
F1	Pass	5.07±0.07	0.143	101.02	5.36±0.23
F2	Pass	5.17±0.8	0.123	100.35	5.08±0.35
F3	Pass	5.45±0.15	0.148	98.96	4.87±0.57
F4	Pass	4.95±0.08	0.156	99.56	5.15±0.65
F5	Pass	4.98±0.07	0.162	102.35	5.38±0.76
F6	Pass	4.87±0.9	0.138	98.96	4.98±0.65
F7	Pass	5.12±0.56	0.149	99.15	5.65±0.87

The variation in weight was within the limit. The thickness of tablets was found to be between 4.9-5.2 mm. The hardness for different formulations was found to be between 5.01 to 5.69 kg/cm2, indicating satisfactory mechanical strength. The friability was<1.0%w/w for all the formulations, which is an indication of good mechanical resistance of the tablet. The drug content was found to be within limits 98 to 102 %.

Table no.05 : Invitro buoyancy studies of carvacrol floating tablets

Formulation Code	Floating Lag Time (sec) N=3	Total floating time N=3	Total floating time N=3
F1	22	Up to 11	+
F2	24	Up to 10	+
F3	30	Up to 12	+
F4	28	Up to 11	+
F5	80	Up to 12	-

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F6	34	Up to 10	-
F7	38	Up to 12	-

Table no.06: % Drug release studies of F1-F7

Time Hrs.	% Drug Release						
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**
0	0	0	0	0	0	0	0
1	22	26	34	20	28	19	23
2	38	42	48	36	40	38	39
4	58	56	63	53	60	59	58
6	76	68	76	70	69	68	72
8	88	75	89	88	78	79	80
10	100	89	100	100	87	86	88
12	100	100	100	100	100	100	100

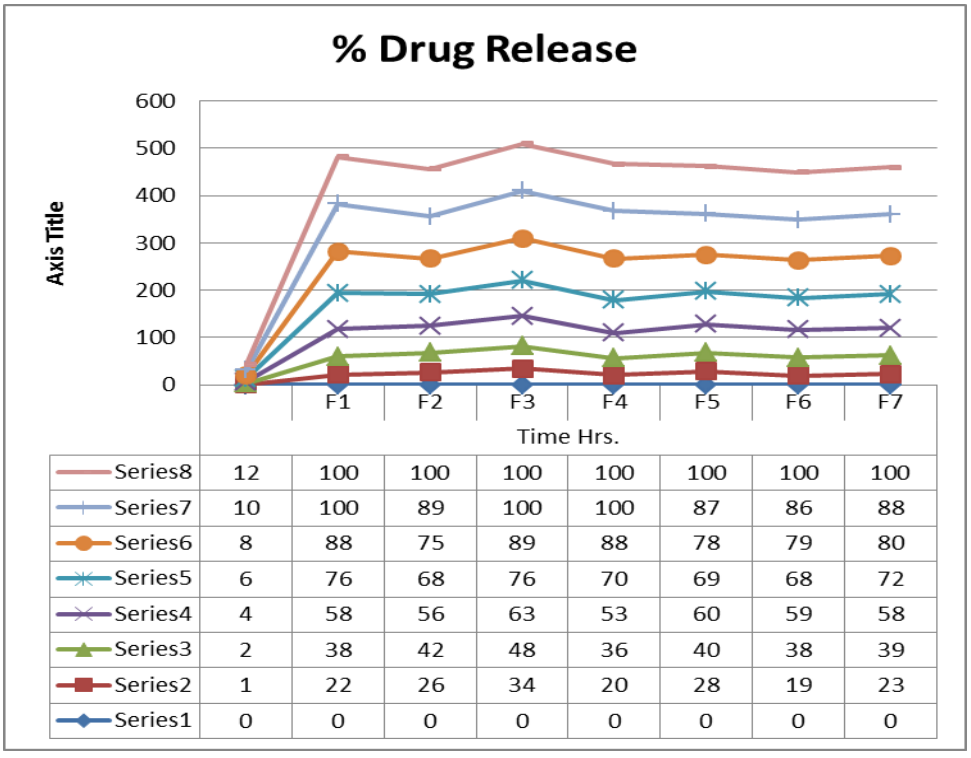

Fig. no. 02: % Drug release studies of F1-F7

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4. Conclusion

The development of a floating drug delivery system (FDDS) for carvacrol to treat Helicobacter pylori infections shows significant promise in overcoming the limitations of conventional antibiotic therapies. The formulated FDDS exhibited excellent buoyancy, ensuring prolonged gastric retention for over 12 hours, and demonstrated a sustained release of carvacrol over 8 hours. These characteristics are crucial for maintaining therapeutic drug levels at the site of infection, enhancing the local action of carvacrol against H. pylori. The antimicrobial efficacy tests confirmed that the FDDS maintained the antimicrobial activity of carvacrol, effectively inhibiting the growth of H. pylori, which highlights the potential of carvacrol as an alternative to traditional antibiotics facing resistance issues. This novel FDDS offers several advantages, including improved patient compliance due to reduced dosing frequency and minimized systemic side effects. The controlled release mechanism ensures consistent therapeutic concentrations, potentially leading to better treatment outcomes. The promising in vitro results warrant further in vivo studies and clinical trials to validate the system's safety and efficacy. Additionally, exploring combinations of carvacrol with other antimicrobials within the FDDS could enhance its effectiveness and broaden its applications. Overall, this study lays a strong foundation for innovative therapies targeting H. pylori, paving the way for more effective and patient-friendly treatments.

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