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FORMULATION AND EVALUATION OF PULSATILE DRUG DELIVERY SYSTEM FOR NOCTURNAL ASTHMA USING *FICUS RELIGIOSA*

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ABSTRACT

Up to 75% of asthmatics experience nocturnal asthma, marked by early morning flare-ups due to increased bronchoconstriction and airway inflammation. Conventional continuous-release medications often fail to provide optimal control during these critical hours. This study aims to develop a Chronomodulated Pulsatile Drug Delivery System (PDDS) using the Pulsincap platform for targeted drug release in sync with circadian rhythms. The system incorporates Ficus religiosa (peepal tree) extracts, known for their anti-inflammatory properties, particularly due to their quercetin content, offering a natural therapeutic approach with minimal side effects.The PDDS features a hydrogel plug to ensure delayed drug release, timed to coincide with peak asthma symptoms. The formulation was optimized through ex vivo pharmacological assessments, stability tests, and in vitro drug release studies, demonstrating effective and consistent drug release at the desired time. The results revealed significant anti-asthmatic potential, stable performance under various conditions, and enhanced symptom control. By combining chronotherapy with herbal medicine, this system improves asthma management by reducing side effects and boosting patient adherence. Moreover, the PDDS platform offers broader potential for treating other circadian-related conditions like rheumatoid arthritis and hypertension, paving the way for tailored, time-specific therapies with improved clinical outcomes.

INTRODUCTION

Oral drug delivery has emerged as the most commonly used and convenient method of administering medications due to its safety, simplicity, and patient acceptance. It includes various dosage forms, such as immediate-release, sustained-release, and controlled-release systems. However, conventional drug delivery systems often fall short in managing diseases with circadian symptom patterns, such as nocturnal asthma, where symptoms worsen at night due to the body's natural biological clock.

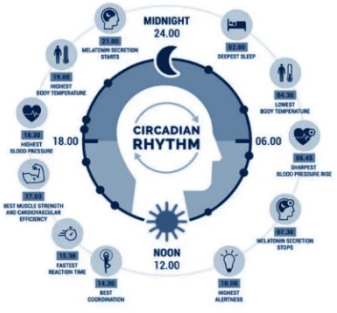


Figure 1.1 Conventional Circadian Rhythm

Circadian Rhythms and Disease Management

The human body follows a 24-hour biological cycle known as the circadian rhythm, regulated by the suprachiasmatic nucleus (SCN) in the hypothalamus. This internal clock synchronizes with environmental cues like light and dark, controlling key physiological processes such as hormone secretion, metabolism, and immune responses. Hormones like melatonin and cortisol exhibit circadian variations, impacting sleep, alertness, and inflammation regulation. Disruptions to these rhythms contribute to chronic illnesses such as asthma, hypertension, and diabetes.1

Diseases like nocturnal asthma show a clear circadian pattern, with symptoms such as wheezing, coughing, and breathlessness peaking during the early morning hours due to increased airway inflammation and bronchoconstriction. This phenomenon underscores the importance of time-specific drug administration, leading to the development of chronotherapy.

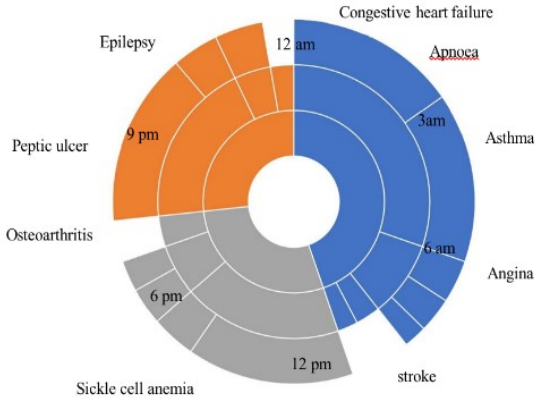


Fig. No. 1.2 Circadian Pattern of Disorders

Chronotherapy: Time-Optimized Treatment

Chronotherapy involves aligning medication administration with the body's biological rhythms to maximize therapeutic effectiveness and minimize side effects. It considers the timing of disease symptoms to optimize drug efficacy. For instance, conditions like asthma, hypertension, and rheumatoid arthritis exhibit circadian symptom patterns, making them ideal candidates for time-targeted therapies.2

In asthma management, chronotherapy can reduce early morning exacerbations by delivering medication during peak symptom hours. Traditional continuous-release formulations fail to provide adequate control due to fixed drug release rates. As a result, there has been a growing interest in developing advanced drug delivery systems capable of releasing medications in sync with the body's internal clock.[3]

Pulsatile Drug Delivery Systems (PDDS)

PDDS have emerged as a revolutionary approach, releasing drugs at specific times rather than continuously. This system is designed with an initial lag phase, followed by a rapid drug release, making it highly effective for conditions with predictable symptom peaks like nocturnal asthma.[4]

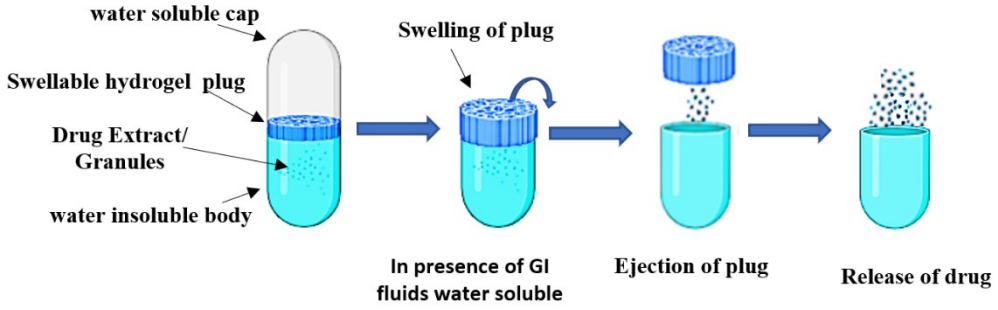


Fig 1.3 Pulsincap technology

- **Types of PDDS:**
  1. **Time-Controlled Systems:** Release drugs after a set lag time, ideal for diseases with a consistent symptom onset pattern.
  2. **Stimuli-Responsive Systems:** Triggered by physiological changes such as pH or temperature fluctuations.
  3. **Externally Regulated Systems:** Controlled by external signals like magnetism or ultrasound.

Among these, the **Pulsincap system** stands out due to its reliability and precision. It consists of a drug-filled capsule sealed with a hydrogel plug. Upon contact with gastrointestinal fluids, the plug swells and is expelled after a predetermined time, releasing the drug precisely when needed. This feature ensures that nocturnal asthma patients receive medication during the early morning hours, reducing symptoms effectively.[5]

***Ficus religiosa*: A Natural Therapeutic Agent**

Ficus religiosa, commonly known as the Peepal tree, has been traditionally used in herbal medicine for treating various ailments, including respiratory conditions like asthma. Its leaves, bark, and fruits contain bioactive compounds such as flavonoids (quercetin), tannins, and phenolics, which exhibit anti-inflammatory, antioxidant, and bronchodilator properties.

Key Phytochemical Actions:

- **Anti-inflammatory Effects:** Quercetin inhibits pro-inflammatory cytokines (e.g., TNF-α, IL-6), reducing airway inflammation.
- **Bronchodilation:** It relaxes airway muscles, improving airflow and reducing asthma symptoms.
- **Histamine Suppression:** It prevents the release of histamine, a major cause of bronchoconstriction.[6]

Research indicates that *Ficus religiosa* extracts can enhance asthma control while minimizing the side effects associated with synthetic drugs. Combining *Ficus religiosa* extracts with PDDS technology creates a synergistic approach for managing nocturnal asthma. The Pulsincap system's time-specific drug release ensures that the plant's anti-inflammatory and bronchodilator effects are maximized during symptom peaks. This approach offers several advantages:

- **Precise Drug Delivery:** Medication is released at the optimal time, ensuring maximum efficacy.
- **Reduced Side Effects:** By targeting symptoms when they are most severe, lower drug doses are required, minimizing adverse effects.
- **Enhanced Patient Compliance:** Once-daily dosing improves adherence and reduces the burden of frequent medication administration.[7]

The integration of time-controlled drug delivery systems with natural therapeutics like *Ficus religiosa* holds immense potential for personalized medicine. Chronotherapy, supported by PDDS and herbal formulations, offers tailored treatment approaches for various circadian-driven conditions, including hypertension, diabetes, and rheumatoid arthritis[8].

In conclusion, combining advanced drug delivery technologies with herbal medicine presents a promising, patient-centric solution for managing nocturnal asthma and other time-sensitive diseases. This approach could pave the way for more effective, safer, and personalized therapeutic strategies.

2. MATERIALS

The materials for the Chronomodulated Pulsatile Drug Delivery System were divided into three stages: **extraction**, **formulation (Hydrogel Plug Formulation and Granulation)**, and **capsule filling and coating**.

1. **Extraction:** Ethanol and methanol served as solvents, and the Soxhlet apparatus was used for extraction. The extract was concentrated using a distillation assembly.
2. **Hydrogel Plug Formulation:** Key components included HPMC K4M and guar gum as polymers for swelling control, lactose as a diluent, and magnesium stearate as a lubricant. The plug was prepared using a compression machine.[9]
3. **Granulation:** Ethyl cellulose was used for controlled release, PVP K30 as a binder, talc as a glidant, and isopropyl alcohol as the granulating fluid.

4. **Capsule Filling and Coating:** Formaldehyde and potassium permanganate were used for crosslinking gelatin capsule shells. Coating was done with Eudragit L100 as the polymer, acetone as the solvent, and polyethylene glycol as the plasticizer to ensure delayed drug release in the intestine.[10]

3.METHODS

The formulation process began with the **extraction of plant material**, where dried and powdered *Ficus religiosa* leaves and bark were subjected to Soxhlet extraction using ethanol and methanol. The extract was concentrated under reduced pressure using a distillation assembly, and the percentage yield was calculated using a standard formula.

For the **evaluation of Pharmacological Activity** [Anti-Asthmatic Activity (*Ex vivo* Method)], Goat tracheal rings were isolated post-slaughter, linked into a chain, and suspended in a Krebs solution bath at 37°C ± 0.5°C with continuous aeration. The dose-response curve (DRC) for histamine was recorded in plain Krebs solution and with 1000 µg/ml Ficus religiosa leaf and bark extract. Atropine served as the standard reference. The contractile response (%) was plotted against histamine concentration to compare its effects with and without the extracts.[11]

In the **hydrogel plug formulation** stage, materials such as HPMC K4M, guar gum, lactose, and magnesium stearate were used. These were mixed and compressed into plugs using a compression machine to create a time-specific swelling mechanism for delayed drug release.

The **granulation process** involved blending ethyl cellulose and PVP K30 with the active extract, followed by wet granulation using isopropyl alcohol. The resulting granules were sieved, dried, and lubricated with talc to ensure proper flow and compressibility.[12]

For **capsule shell treatment**, size 0 hard gelatin capsules were treated with formaldehyde vapor in the presence of potassium permanganate to achieve crosslinking, ensuring delayed release in gastric conditions. These capsules were dried in a desiccator for 24 hours.

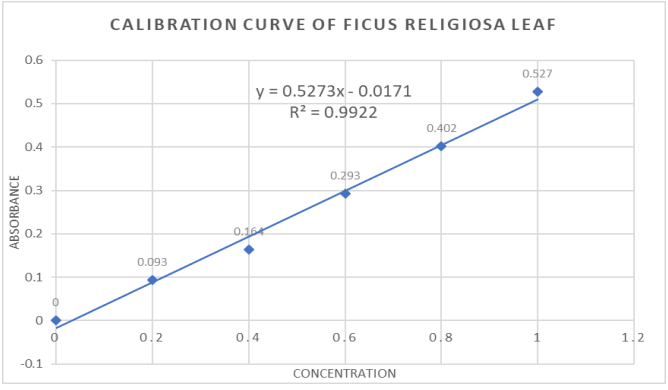
The final step was the **coating of capsules**, which used Eudragit L100 as the polymer, acetone as the solvent, and polyethylene glycol as the plasticizer. This coating provided enteric properties, allowing the drug to release in the intestinal region. Drug release profiles were tested using a dissolution apparatus, and cumulative release percentages were calculated over time.[10,13]

4.RESULTS AND DISCUSSION

The selection of *Ficus religiosa* was based on its known anti-asthmatic properties due to bioactive constituents like flavonoids and tannins. Authentication confirmed its identity through morphological and microscopic evaluation. Extraction using ethanol and methanol yielded 9.8g and 4g respectively. Phytochemical screening confirmed the presence of carbohydrates, glycosides, alkaloids, flavonoids, tannins, and phenols in both extracts.

- **Pre-Formulation Studies.**
  1. Melting Points: Leaf extract: 122°C, Bark extract: 132°C.
  2. λmax Values: Leaf extract: 267.8 nm, Bark extract: 203 nm.
  3. Calibration Curves: Both extracts showed strong linearity with R^2 values of 0.995 (leaf) and 0.996 (bark).

A.



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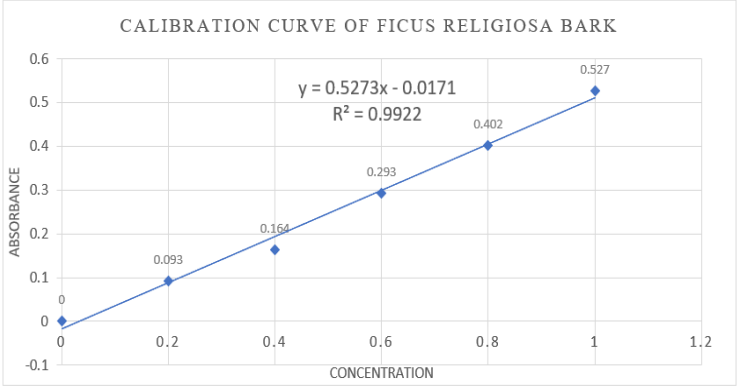
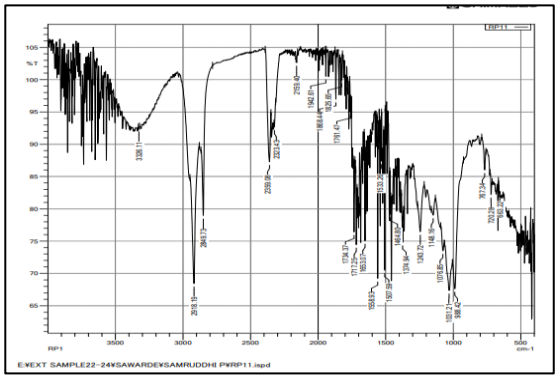


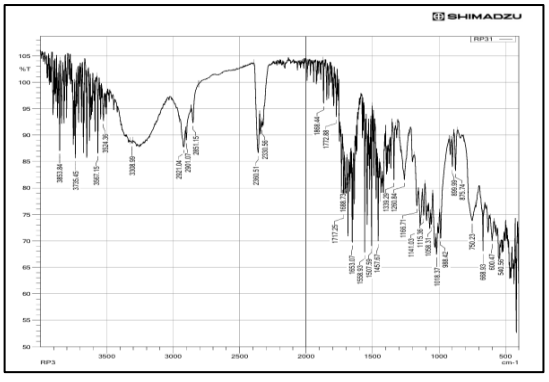
Fig. 4.1 A. calibration curve for *ficus religiosa* leaf,
B. Calibration Curve for *Ficus religiosa* bark

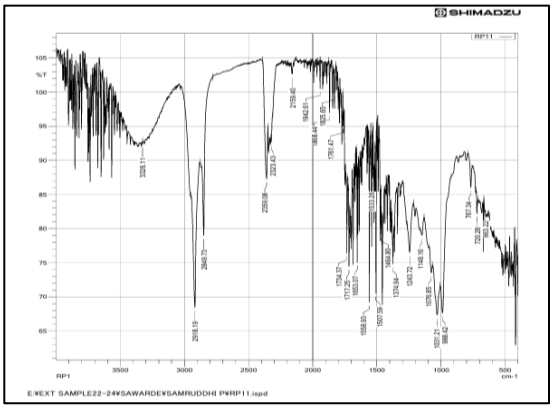
4. Solubility Studies: Ethanol and methanol had the highest solubility (93-95%).

Compatibility Studies

FTIR and DSC confirmed no significant interactions between the extracts and excipients, supporting stability in the formulation.







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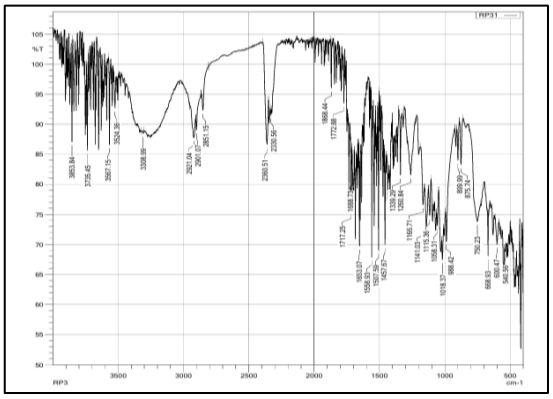
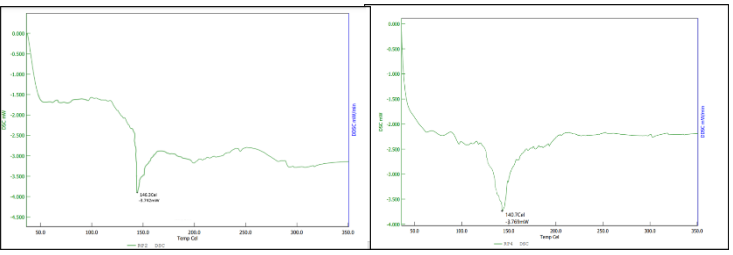
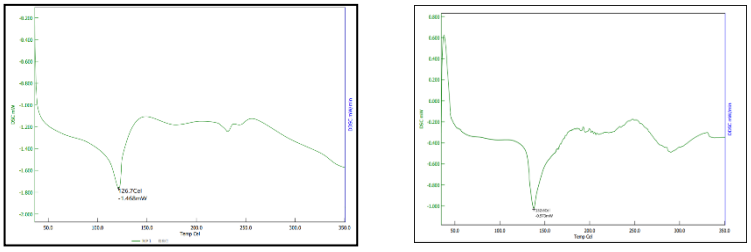


D

Fig. 4.2 FTIR Spectra A. *Ficus religiosa* Leaf extract, B. Physical mixture containing *Ficus religiosa* leaf extract with excipients, C. *Ficus religiosa* Bark extract, D. Physical mixture containing *Ficus religiosa* bark extract with excipients



A B



C D

Fig. 4.3 DSC Thermograms A. *Ficus religiosa* Leaf extract, B. Physical mixture containing *Ficus religiosa* leaf extract with excipients, C. *Ficus religiosa* Bark extract, D. Physical mixture containing *Ficus religiosa* bark extract with excipients.

Pharmacological Activity Evaluation

Goat trachea studies showed significant inhibition of histamine-induced contractions. Atropine (standard drug) achieved 100% inhibition, while leaf and bark extracts showed 98.33% and 96.7% inhibition, respectively.

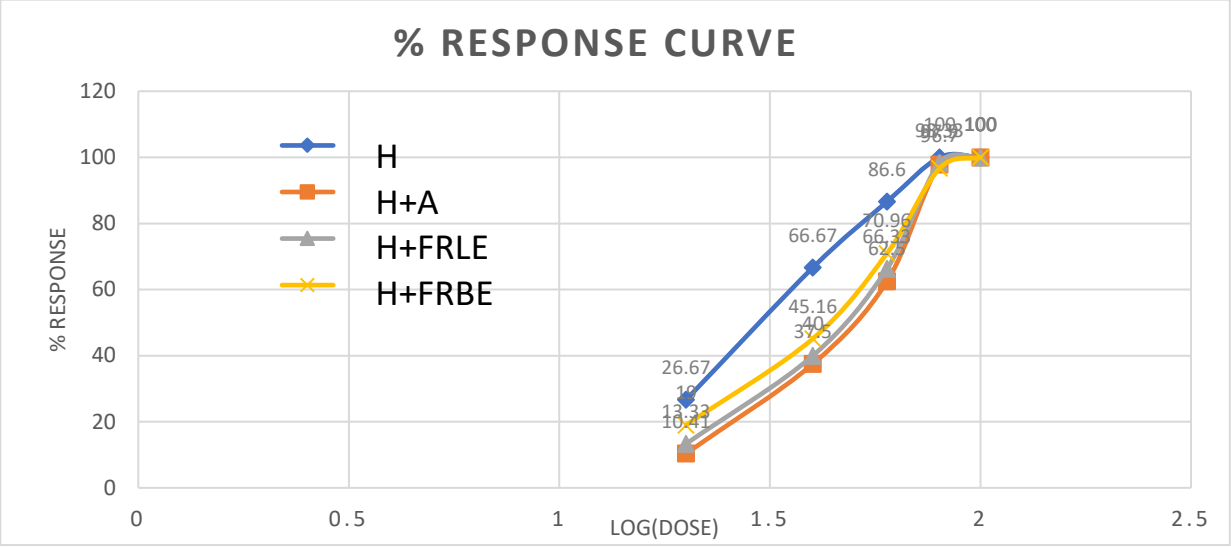
Table No. 1 Calculation table for log dose and percent response

Sr.no.	Dose (ml)	Dose (µg)	Log Dose	%Response			
				H(Histamine)	H+A(Atropine)	H+FRLE	H+FRBE
1	0.2	20	1.301	26.67	10.41	13.33	19.00
2	0.4	40	1.602	66.67	37.5	40.00	45.16
3	0.6	60	1.778	86.6	62.5	66.33	70.96
4	0.8	80	1.903	100	97.9	98.33	96.7
5	1.0	100	2	100	100	100	100

%Response = (Height of Peak /Maximum Height of Peak) X 100

- **Atropine** (H + A) showed dose-dependent inhibition of histamine-induced contractions, reaching 97.9% at 80 µg and 100% at 100 µg.
- The leaf extract (**FRLE**) produced slightly higher inhibition compared to the bark extract (**FRBE**), with a maximum of 98.33% at 80 µg.

Fig. 4.4 Graph of Percent Response Curve



Hydrogel Plug Evaluation

Table No. 2 Formulation Table for hydrogel plug

Ingredients (mg)	Role	Formulations					
		H1	H2	**H3**	H4	H5	H6
HPMC K4m	Polymer	20 mg	30 mg	**40 mg**	-	-	-
Gaur Gum	Polymer	-	-	**-**	20 mg	30 mg	40 mg
Lactose	Diluent	158 mg	148 mg	**138**	158 mg	148 mg	138 mg
Magnesium Stearate	Lubricant	2 mg	2 mg	**2 mg**	2 mg	2 mg	2 mg

Table No. 3 Evaluation Table for hydrogel plug

Parameter	H1	H2	H3	H4	H4	H6
Hardness (kg/cm²)	4±0.3	5±0.07	**6±0.10**	3±0.15	4±0.15	5±0.1
Thickness (mm)	4±0.02	4±0.05	**4±0.03**	4±0.02	4±0.02	4±0.04
Weight variation(mg)	180±0.2	180± 0.3	**180± 0.2**	180±0.4	180±03	180±0.2
Lag time (min)	272±0.5	366±0.5	**415±0.5**	265±0.5	338±0.5	389±0.5
Lag time (hours)	4 hours 53 mins	6 hours 6 mins	**6 hours 55 mins**	4 hours 25 mins	5 hours 38 mins	6 hours 28 mins

- Best Formulation: H3 (HPMC-based) with hardness: 6±0.1 kg/cm² and lag time: 415±0.5 min.
- Swelling Index: Highest in pH 6.8 buffer, indicating controlled swelling.

Ingredients (mg)	Role	Formulations		
		G 1	G 2	G 3
Ficus religiosa Leaf Extract	API	(33.3%)100 mg	(33.3%)100 mg	(33.3%)100 mg
Lactose	Diluent	(44%) 131mg	(44%) 116 mg	(44%) 101 mg
Ethyl Cellulose	**Polymer**	**(10%) 30 mg**	**(15%) 45 mg**	**(20%) 60**

PVP K30	Binder	(10%) 30 mg	(10%) 30mg	(10%) 30
Talc	Glidant	(2%) 6 mg	(2%) 6mg	(2%) 6
Magnesium stearate	Lubricant	(1%) 3 mg	(1%) 3 mg	(1%) 3
Isopropyl Alcohol	Granulating solvent	QS	QS	QS

Granule Evaluation

Table No. 4 Formulation Table for granules.

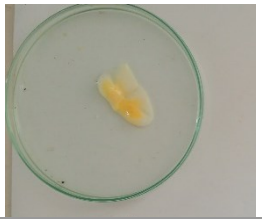
- Micromeritics: G2 showed the best flow properties (Angle of Repose: 25.24°, Carr's Index: 13.18%, Hausner's Ratio: 1.16).
- Drug Content: G2 exhibited the highest assay value (98.12%) with a moderate disintegration time (2500 sec).

Thus, **G2** is the optimal formulation, offering both adequate release timing and superior drug content for consistent therapeutic outcomes.

Pulsincap System Evaluation

Table No. 5 Observation Table for formaldehyde treatment of capsules

Table No. 6 Weight Specifications of pulsincap system

Sr. no.	Capsule Type	Solubility Test	
1	Formaldehyde untreated capsules without coating	Whole capsule ≤15 mins	
2	Formaldehyde treated capsules without coating	Cap ≤15 mins Body – 10 hours	

- Formaldehyde Treatment: Capsule shells remained intact for 24 hours after treatment, ensuring delayed release.
- Weight Specifications: Capsules ranged from 0.65-0.69g after coating.

***InVitro* Drug Release**

Sr. No.	Dissolution Medium	Time (hrs.)	% Cumulative Drug Release			
			F1	F2	F3	F4
Formulation			**F1(g)**	**F2 (g)**	**F3 (g)**	**F4 (g)**
Empty capsule weight			0.08 g	0.08 g	0.08 g	0.08 g
Capsules with granules			0.36 g	0.35 g	0.33 g	0.37 g
Capsule with hydrogel plug			0.54 g	0.54 g	0.55 g	0.56 g
Sealed capsule			0.59 g	0.62 g	0.61 g	0.61 g
Coated capsule			0.68 g	0.65 g	0.69 g	0.67 g
Total weight of dried capsule			0.65 g	0.61 g	0.65 g	0.66 g

1	0.1 HCl pH 1.2	1	0	0	0	0
2		2	0	0	0	0
3		3	0.31164	0	0.093	0
4	7.4 pH Phosphate buffer	4	0.84588	0.09	0.4185	0.0438
5		5	2.27052	0.405	1.2555	0.1314
6		6	6.2328	0.99	3.348	0.9198
7	6.8 pH Phosphate Buffer	7	10.64028	2.025	8.091	3.7668
8		8	18.4758	8.685	14.9265	10.512
9		9	28.89348	20.655	27.5745	23.1264
10		10	45.23232	38.07	45.942	38.7192
11		11	64.42044	60.48	66.5415	60.225
12		12	89.61876	90	91.3725	87.0744

Table No. 7. Observations of *Invitro* drug release.

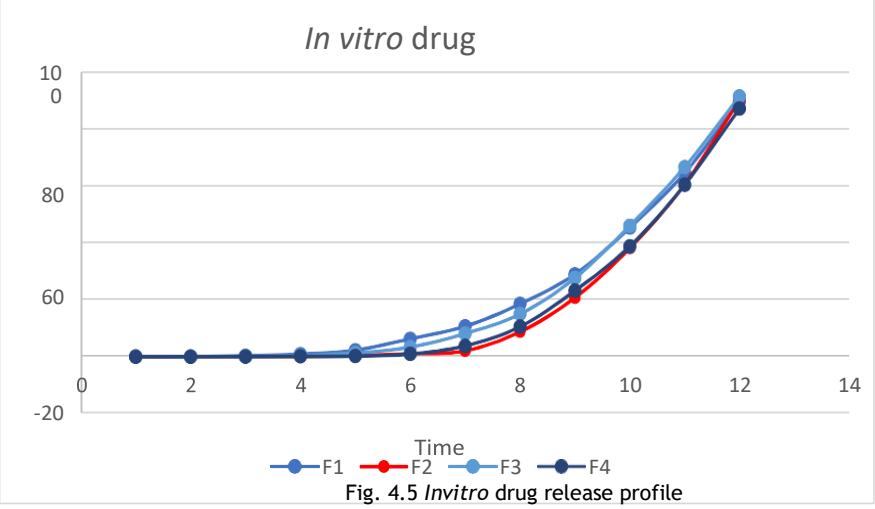


Fig. 4.5 *Invitro* drug release profile

Optimal Formulation: F2 reached 90% cumulative drug release at 12 hours, ensuring controlled and prolonged drug availability. No drug was released at pH 1.2, confirming enteric coating efficiency.

The optimized formulation (F2) with *Ficus religiosa* extracts demonstrated excellent stability, delayed release, and significant anti-asthmatic potential, making it ideal for managing nocturnal asthma.

The study demonstrated that *Ficus religiosa* extracts possess strong anti-asthmatic properties due to flavonoids and tannins. Ethanol extraction yielded higher bioactive content. Compatibility studies confirmed formulation stability. **Ex vivo studies** demonstrated that the **ethanolic leaf extract** produced a stronger anti-asthmatic response than the bark extract, making it the preferred candidate for further formulation.

The H3 hydrogel plug (HPMC-based) showed optimal lag time (415 min), ensuring time-specific drug release. Granules (G2) exhibited excellent flow, compressibility, and drug content (98.12%). Formaldehyde-treated capsules provided delayed release, while F2 formulation achieved controlled drug release (90% in 12 hours), proving ideal for nocturnal asthma management.

The study successfully developed a **Chronomodulated Pulsatile Drug Delivery System (PDDS)** using **Ficus religiosa** extracts for nocturnal asthma management.

CONCLUSION

The chronomodulated delivery system effectively aligns drug release with circadian asthma symptom peaks, ensuring medication availability during early morning exacerbations. Ficus religiosa extracts offer anti-inflammatory and bronchodilatory effects, reducing symptoms with fewer side effects. Compared to existing treatments, the system provides time-specific drug release, enhancing therapeutic efficiency while minimizing dosing frequency. Clinically, this approach improves patient compliance and symptom management through prolonged, targeted action. Challenges include optimizing large-scale production, ensuring consistent drug release profiles, and conducting clinical trials. Future research could explore advanced polymers and combination therapies. In conclusion, the study highlights Ficus religiosa's potential in a pulsatile drug delivery system, offering a promising, patient-centered treatment for nocturnal asthma with enhanced therapeutic outcomes.

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