RESEARCH PAPER

DESIGN DEVELOPMENT AND VALIDATION OF PULSATILE DRUG DELIVERY SYSTEM FOR CHRONOTHERAPEUTIC APPLICATION

Hole G.A.[1*], Sawale A.V.[1], Vyas L.K.[2], Motwani A.N.[1], Pote S.S.[1], Pachghare B.P.[1], Shelke S.U.[1]

[1]Department of Pharmaceutical Quality Assurance, Vidyabharti College of Pharmacy, Amravati, Maharashtra 444 603.

[2]Department of Cosmetic Technology, Vidyabharti Mahavidyalaya Camp, Amravati, Maharashtra 444 603.

***Corresponding author: Hole G.A., Department of Pharmaceutical Quality Assurance, Vidyabharti College of Pharmacy, Amravati, Maharashtra 444 603**

Email: gayatrihole8@gmail.com

Received: 28th April, 2026; **Revised:** 12th May, 2026; **Accepted:** 26th May, 2026; **Available Online:** 19th June, 2026

ABSTRACT

Pulsatile Drug Delivery Systems (PDDS) are designed to release drugs after a predetermined lag time followed by rapid release, making them particularly suitable for the chronotherapeutic management of diseases exhibiting circadian variation in symptom intensity. The present study aimed to develop and evaluate a pulsatile Bilastine drug delivery system for allergic rhinitis, a condition in which symptoms such as sneezing, nasal congestion, and itching are most severe during the early morning hours. Preformulation studies, including melting point, solubility, and UV spectrophotometric analysis, were conducted to characterize Bilastine. The λmax of Bilastine in methanol was found to be 218 nm. Core tablets were prepared by direct compression using suitable diluents, super disintegrants, and lubricants. The optimized core formulation (C3) exhibited satisfactory physicochemical properties with 99.85% drug release within 5 hours. These cores were further press-coated with Ethyl Cellulose, HPMC, and Carbopol to achieve the desired lag time followed by rapid release. The optimized press-coated formulation demonstrated a lag time of approximately 7 hours, releasing 98.40% of Bilastine thereafter. The validated HPLC method confirmed excellent reproducibility. Overall, the formulation showed effective pulsatile release and represents a promising approach for improving the chronotherapeutic management of allergic rhinitis.

Keywords: Chrono-pharmacology, Pulsatile drug delivery system, Pulsatile tablet.

How to cite this article: Hole GA, Sawale AV, Vyas LK, Motwani AN, Pote SS, Pachghare BP, Shelke SU. Design Development and Validation of Pulsatile Drug Delivery System for Chronotherapeutic Application. Int J Drug Deliv Technol. 2026;16(61s):1339-1348. DOI: 10.25258/ijddt.16.61s.152

Source of support: Nil.

Conflict of interest: None

INTRODUCTION:

Pharmaceutical technology advancements have led to an increase in the popularity of novel medication delivery systems in recent decades. Current pharmaceutical research focuses more on improving the delivery systems of already-approved drugs than on discovering new compounds.[1] Conventional sustained-release systems maintain drug concentration within the therapeutic window for a significant period of time. However, because they have circadian rhythms, living things do not necessarily require constant medication delivery.[2] Although sustained-release formulations were once thought to be beneficial, they are inappropriate for certain medications due to first-pass metabolism, drug tolerance, toxicity, and decreased patient compliance from repeated administration.[3] In these cases, it is better to distribute drugs at a specific time. This led to the development of chrono pharmaceutics, which aims to enhance treatment outcomes by designing drug delivery systems in accordance with biological cycles. For conditions requiring rapid and transient drug release after a predetermined lag time, these techniques are particularly useful when conventional sustained-release formulations are unable to provide adequate therapeutic efficacy. Drug delivery at a particular time point is more advantageous in these situations. Chrono pharmaceutics, which aims to improve therapeutic outcomes by designing drug delivery systems in accordance with biological rhythms, emerged as a result.[4]

MATERIALS AND METHOD:

Reagents and Chemicals: To formulate the Bilastine tablets, the active pharmaceutical ingredient (API) Bilastine was Obtained from SM Pharma, The excipients used in the formulation , including microcrystalline cellulose (MCC PH 102), polyvinylpyrrolidone (PVP K-30), sodium starch glycolate, talc, magnesium stearate, hydroxypropyl methylcellulose (HPMC K100M), lactose, and Carbopol, were procured from the laboratory of VBCOP, methanol, formic acid and water used for HPLC analysis were of HPLC

grade. All other chemicals and reagents used in the study were of analytical grade.

Instrument and equipment: FTIR analysis was performed using an FTIR spectrophotometer (Shimadzu, Japan) UV spectroscopic analysis was carried out using a UV–Visible spectrophotometer (UV-1800, Shimadzu Corporation, Japan). Chromatographic analysis was performed using Shimadzu RP-HPLC system equipped with Column: Zodiac C18 5µ, (150 X 4.6 mm. ID)

PREFORMULATION:

Organoleptic property: The Bilastine sample was evaluated visually for appearance, colour, and odour.

Solubility: The solubility of Bilastine is assessed using a semi-quantitative method. Small amounts of the drug are progressively combined with a fixed volume of different solvents, such as distilled water, methanol, and dimethyl sulphoxide. After each addition, the mixture is thoroughly shaken, and any particles that have not dissolved are examined visually.

Melting point: The melting point is determined using the capillary tube.

λ max: A UV double beam spectrophotometer is used to scan a standard solution of Bilastine in order to determine its absorption maximum (λmax). A 10 µg/mL solution is made in methanol and scanned between 200 and 400 nm in wavelength.

FTIR Analysis: Identification of Bilastine carried out by infrared Spectroscopy.

Evaluation of powder blend [5-9]

Angle of Repose: The angle of repose was determined by the funnel method

Bulk Density: Bulk density was measured as the ratio of powder mass to bulk volume

Tapped density: Tapped density was determined by tapping the graduated cylinder

Carr's Compressibility Index: Carr's index was calculated to determined compressibility and flow characteristics of the blend.

Hausner's Ratio: Hausner's ratio was calculated from bulk and tapped density to assess powder flowability.

Preparation and Evaluation of Pulsatile tablet

Prepartation of core tablets: Bilastine 20 mg core tablets were prepared by direct compression using lactose, microcrystalline cellulose, starch, crospovidone, PVP K-30, talc, and magnesium stearate. The blend was evaluated for flow properties and compressed with a 9 mm punch.

Table 1: Composition of batches of Core tablets

Ingredients in (mg) tab	Function	Batch 1	Batch 2	Batch 3	Batch 4	Batch 5
Bilastine	API	20	20	20	20	20
Microcrystalline cellulose (MCC)	Diluent	85	85	50	70	90
Lactose	Diluent	-	-	30	-	10
Magnesium Stearate	Lubricant	5	5	5	8	2
Talc	Glidant	5	5	5	7	3
PVP K-30	Binder	10	15	10	10	10
Starch	Disintegrant	25	20	30	35	15
Total weight		150	150	150	150	150

Preparation of Press-Coated Tablets

A tablet compression machine was used to prepare press-coated tablets using the direct compression method. The Bilastine core tablet was positioned in the center of the die cavity after half of the coating blend had been added. The remaining coating blend was then added. A 5mm punch was used to compress the tablets.

Table No 2: Composition of batches of Press-coated tablets

Ingredients in (mg) tab	Function	Batch 1	Batch 2	Batch 3	Batch 4	Batch 5
HPMC 120 100 60	Swellable Polymer	200	120	120	160	100
Ethyl Cellulose	Release Retardant	–	80	–	–	60
Carbopol	Swellable Polymer	–	–	80	40	60
Microcrystalline cellulose (MCC)	Diluent	80	80	80	80	70
Talc	Glidant	10	10	10	10	5
Magnesium Stearate	Lubricant	10	10	10	10	5
Total Weight		300	300	300	300	300

Evaluation of Core and Press-Coated Pulsatile Tablets [10-13]

Tablet Thickness and Size: Thickness and diameter of tablets is measured using a vernier caliper to ensure uniformity.

Tablet Hradness: Hardness of tablets is determined using a Pfizer hardness tester and expressed in kg/cm^2.

Friability: A Roche friabilator operating at 25 rpm for four minutes is used to assess friability, and the percentage of weight loss are computed.

Weight Variation Test: To assess weight uniformity in accordance with IP specifications, twenty tablets are weighted separately, and the average weight is computed.

Uniformity of Weight: Twenty tablets are weighted individually, and weight variation are compared with IP standards.

Drug Content: By dissolving powdered tablets in methanol and measuring absorbance at 218 nm, the drug content can be ascertained.

Disintegration Study: The USP disintergration apparatus is used to measure the disintergration time in pH 6.8 phosphate buffer at 37± 7°C.

In Vitro Drug Release Studies: Dissolution studies in pH 6.8 phosphate buffer at 37 ± 0.2°C and 50 rpm are performed using USP Type II paddle apparatus.

HPLC Method Development and Validation: [14-15]

Selection of Column: The Zodiac C18 column provides a symmetric peak. Acceptable therapeutic plates (≈3200) and good resolution.

Selection of Mobile Phase: The Zodiac C18 column was chosen for the optimized method since it demonstrated improved peak symmetry, acceptable theoretical plates

Preparation of Standard Stock Solution: A standard stock solution of Bilastine (1000 µg/mL) was prepared using acetonitrile, methanol, and water (3:6:1, v/v).

Preparation of working standard solution: The stock solution is appropriately diluted using the same solvent system to create the working standard solution of 100 µg/ml.

Selection of Flow Rate: Different flow rates were evaluated and the optimized flow rate is selected based on maximum column efficiency, good resolution and shorter run time.

Selection of Wavelength: Although Bilastine showed maximum absorbance at 218 nm, 252 nm was selected due to better peak purity, lower interference, and improved baseline stability.

Different Method Development Trials

Developed Method Chromatographic parameter

1. Analytes: Bilastine
2. Column: Zodiac C18 5µ, (150 X 4.6 mm. ID.)
3. Mobile Phase: 0.1% formic acid - acetonitrile (80:20% v/v)

Method Validation

Selectivity: Spectrum from blank and sample (100) ppm both are recorded

Repeatability: Six consecutive injections of the standard solution of Bilastine (100 ppm) were used to measure repeatability,

System Sutability: System suitability parameters like theoretical plates, tailing factor, resolution, and %RSD are assessed.

Precision: Intraday Precision: Analysis performed at different times on the same day, Interday Precision: Analysis performed on three different days.

Robustness: Small, intentional adjustments to flow rate, mobile phase composition, and wavelength are used to assess robustness.

Linearity: A calibration curve was plotted after linearity was established over the concentration range of 6.25–100 ppm.

Limit of Detection (LOD) and Limit of Quantification (LOQ): LOD and LOQ is determined using serial dilutions of Bilastine standard solutions prepared from stock solution.

Accuracy: Recovery studies employing the standard addition method at concentration levels of 80%, 100%, and 120% are used to assess accuracy.

RESULTS AND DISCUSSION:

Preformulation Studies

Organoleptic Properties: Bilastine was observed as a white, odorless powder.

4.1.2 Melting Point: The melting point was found within the reported range of 192°C – 194°C

Solubility Analysis: Bilastine is practically insoluble in water, very slightly soluble in dimethyl sulfoxide, and freely slightly soluble in methanol.

FTIR Analysis: Table No.3: FTIR Spectroscopy Interpretation Bilastine (API)

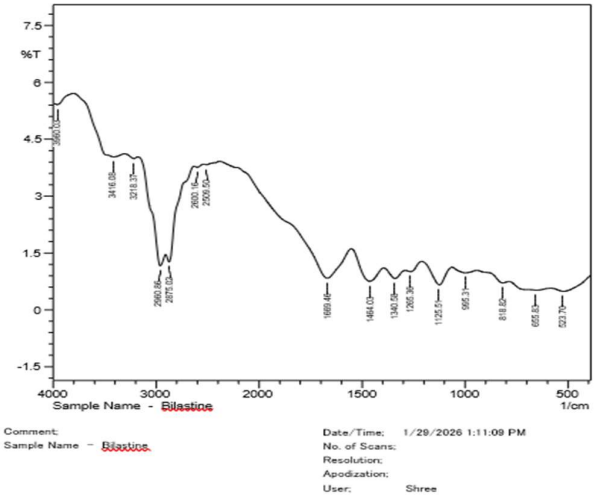


Fig No.1: FTIR of Bilastine

Batch	Weight Variation (mg)	Hardness (kg/cm²)				Friability (%)	Thickness (mm)	Drug Content (%)	Disintegration Time (sec)
		Sr. No.	Peak (cm^{-1})	Functional Group Interpretation	Interpretation				
		1	3416	N–H stretching	Amine group				
		2	2960	C–H stretching	Aliphatic (CH_3/CH_2)				
		3	1689	C=O stretching	Carboxylic acid				
		4	1464	C–H bending	Alkane / aromatic				
		5	1256	C–O stretching	Alcohol / ether				
		6	1125	C–O stretching	Ether linkage				
		7	818	C–H bending	Aromatic ring				
		8	655	C–Cl stretching	Halogen group				
C1	150 ±1.3	3.5 ± 0.35				0.94	3.0 ± 0.50	95.66	43 ± 1.12
C2	150 ±1.4	3.0 ± 0.47				0.92	3.1 ± 0.22	96.12	41 ± 1.51
C3	150 ±1.2	3.5 ± 0.52				0.98	3.0 ± 0.28	98.05	30 ± 0.50
C4	149 ±1.5	3.8 ± 0.40				0.88	3.2 ± 0.28	97.10	28 ± 0.65
C5	150 ±1.1	4.0 ± 0.45				0.85	3.3 ± 0.30	96.72	25 0.72

Determination of λ max: The λ-max of Bilastine was determined using a UV-visible spectrophotometer and was found to be 218 nm.

Table No.4: Maximum Wavelength of Bilastine (API)

Sr. No	Wavelength (nm)	Average
1	218	218
2	217	
3	219	

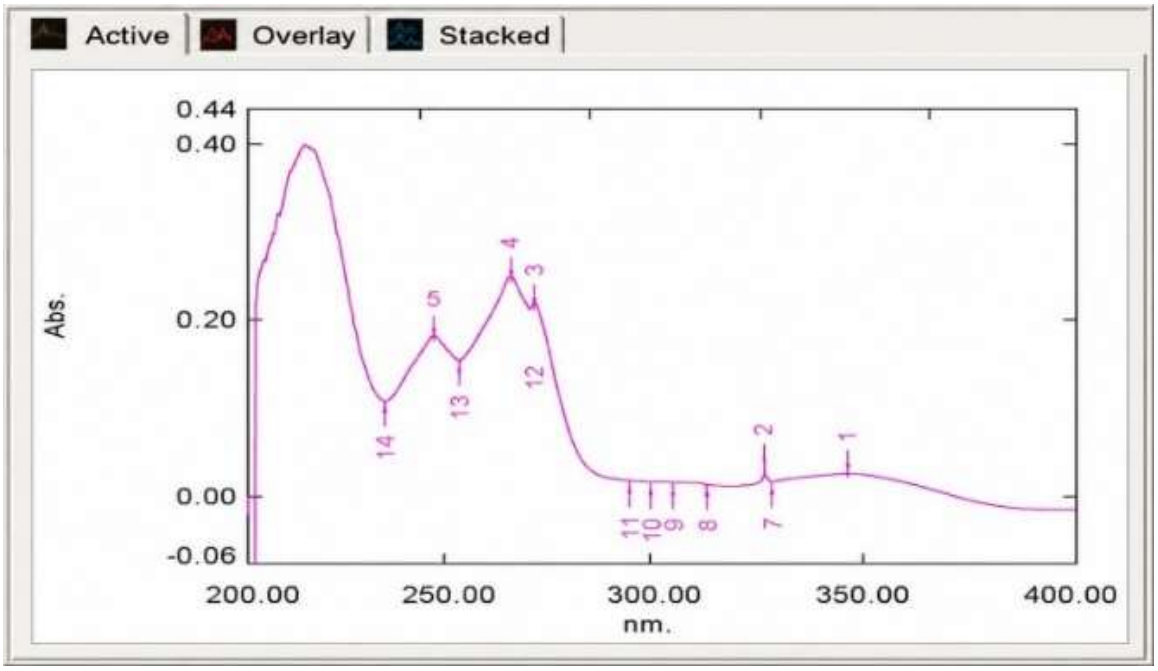


Fig No.2: Determination of UV of Bilastine (API)

Calibration Curve:

The calibration curve showed linearity in the concentration range of 2–10 µg/mL with the regression equation y = 0.028x + 0.038 and a correlation coefficient (R^2) of 0.9949

Table No.5: Calibration curve of Bilastine in Methanol

Sr. No.	Concentration (µg/ml)	Absorbance
1.	2	0.10
2.	4	0.14
3.	6	0.21
4.	8	0.26
5.	10	0.32

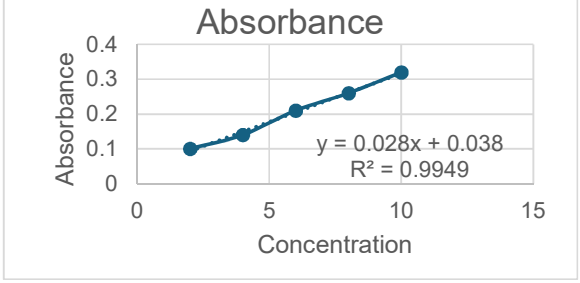


Fig No.3 : Calibration Curve of Bilastine in Methanol

Pre-compression parameter of core and press coated tablet

Pre-compression evaluation of Bilastine was carried out to determine its flow and compressibility characteristics prior to formulation development.

Table No.6: Pre - compression Parameters for Core Formulation

Table 7: Post compression parameter of core and press coated Pulsatile tablet

Sr. No	Parameter	Results				
		C-1	C-2	C-3	C-4	C-5
1	Bulk density	0.41 ± 0.02	0.42±0.01	0.40 ± 0.02	0.43 ± 0.01	0.44 ± 0.02
2	Tapped density	0.49± 0.01	0.50±0.02	0.47 ± 0.01	0.51 ± 0.02	0.52 ± 0.01
3	Cars index	16.33 ±0.41	16.00±0.41	14.89±0.35	15.69± 0.32	15.38± 0.29
4	Hausner's ratio	1.20 ± 0.02	19 ± 0.01	1.18 ± 0.01	1.18 ± 0.02	1.18 ± 0.01
5	Angle of repose	27.42 ±0.31	28.16±0.24		26.83 ±0.27	27.65± 0.18	26.24± 0.22

Post compression parameter of core and press coated pulsatile tablet

Weight Variation: All formulations (C1–C5) complied with Pharmacopoeial limits.

Hardness: Tablet hardness was within acceptable range, indicating good mechanical strength.

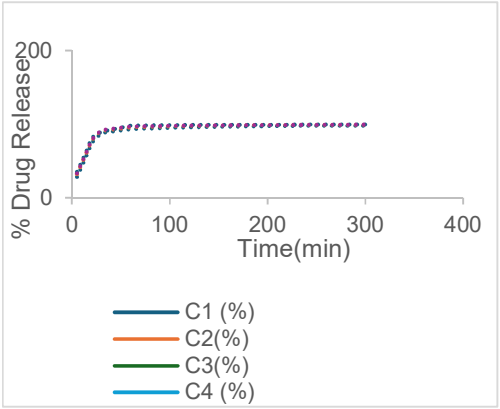
Friability: Friability values were below 1%, showing adequate tablet strength.

Drug Content: Drug content was found within acceptable limits, indicating uniformity.

Thickness: Tablet thickness was uniform for all batches.

Disintegration Time: All formulations showed acceptable disintegration time, with C3 showing the fastest disintegration.

Dissolution Study: In vitro drug release in pH 6.8 phosphate buffer for up to 300 minutes was assessed for the optimized batch (C3). By the end of the study, the formulation had achieved nearly full drug release (~99%) with a controlled and gradual release pattern. With an initial lag followed by sustained drug release,



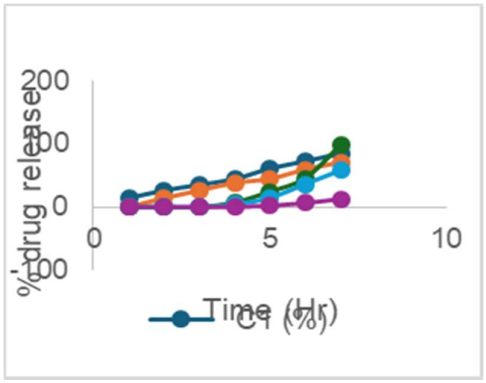


Fig No.4: % Drug Release of core tablet **Fig No.5 : % Drug Release of press-coated tablet**

Table No.8 : In vitro drug release of core tablet Bilastine

Time (min)	C1 (%)	C2 (%)	C3 (%)	C4 (%)	C5 (%)
5	28.45	32.18	35.62	30.75	33.40
10	42.60	46.85	49.20	45.10	47.75
15	58.72	62.30	65.48	60.95	63.12
20	74.85	78.60	82.15	77.20	79.05
30	88.40	91.25	90.01	90.35	92.18
60	93.75	96.10	98.25	95.80	97.05
120	96.20	98.05	99.10	97.85	98.60
180	97.10	98.75	99.45	98.60	99.05
240	97.85	99.10	99.70	99.05	99.40
300	98.20	99.35	99.85	99.40	99.65

Table No.9: Evaluation of Press-Coated Pulsatile Tablets of Bilastine (C1 to C5)

Batch	Weight Variation (mg)	Hardness (Kg/cm²)	Friability (%)	Thickness (mm)	Drug Content (%)	Lag Time (Hr)
C1	351±0.28	5.9±0.35	0.58	4.52±0.42	97.85	1
C2	353±0.31	6.1±0.40	0.55	4.55±0.36	98.20	2
C3	352±0.26	6.3±0.38	0.49	4.51±0.30	98.10	4
C4	350±0.34	6.0±0.29	0.53	4.53±0.41	97.90	3
C5	354±0.29	6.2±0.33	0.51	4.54±0.41	98.65	4

Table No.10 : In-vitro Drug Release of Press-Coated Pulsatile Tablets of Bilastine (C1 to C5)

Time (Hr)	C1 (%)	C2 (%)	C3 (%)	C4 (%)	C5 (%)
1	14.29	0	0	0	0
2	26.36	14.29	0	0	0
3	35.26	26.36	0	0	0
4	44.35	38.42	7.35	4.20	0
5	61.20	44.79	24.60	14.80	1.95
6	72.50	59.65	45.75	36.45	6.30
7	85.10	70.96	98.40	58.20	12.85

HPLC Method Development and Validation:

Method Development: Optimized conditions selected were a Zodiac C8 column (150 × 4.6 mm, 5 µm), 0.1% formic acid–acetonitrile (80:20, v/v) as the mobile phase, a flow rate of 1.0 mL/min, and detection at 252 nm.

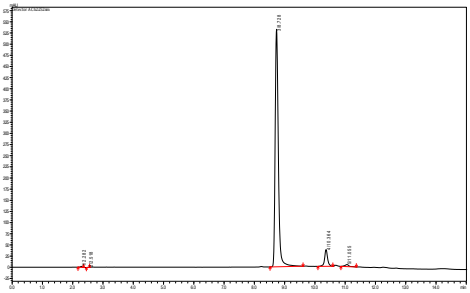
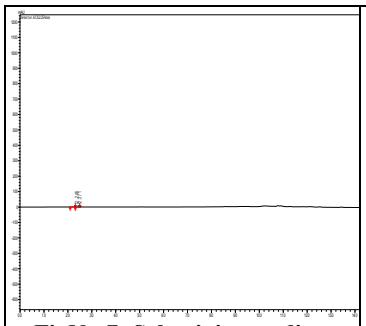


Fig No.6: Method development of Bilastine by RP-HPLC

Selectivity: After comparing the retention times of separated API and developed formulation with blank sample analysis,

Repeatability: The mean peak area of Bilastine (100 ppm) was found to be 4,034,466 with a standard deviation of 50,450.97.



FigNo.7: Selectivity studies; blank sample

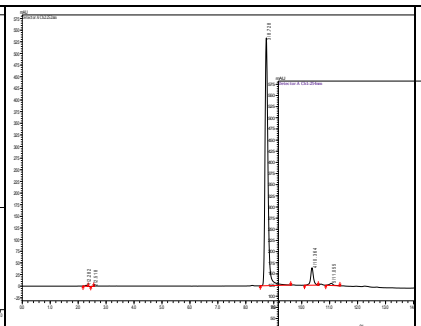
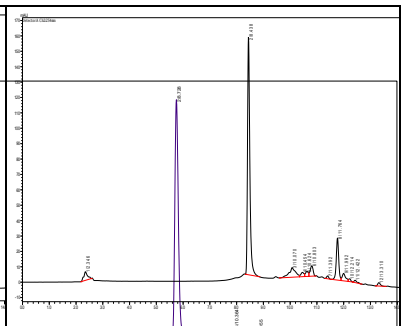


Fig No.8: Selectivity studies; Bilastine API



FigNo.9: Selectivity Studies; Developed formulatation

Table No.11: Repeatability study of Bilastine

Fig No.10: Repeatability study of Bilastine by RP-HPLC

Sr. No.	Drug Name; **Bilastine**
	Peak Area; Conc. 100 ppm
1	3943199
2	4061361
3	4034443

System suitability	Bilastine	Acceptance
Theoretical plates (*N*)	34041	≤ 2000
Capacity Factor (*K'*)	3.84	≤ 0.5
Resolution (*R*)	---	≤ 1.5
Separation factor (α)	1.08	> k'
Tailing factor (*T*)	1.24	< 1.5
Retention time (t_R)	8.72 min.	> k'
Wavelength (nm)	252 nm	> 200 nm
Repeatability (% RSD)	1.25%	< 2%
Intra-Day Precision (% RSD)	0.83-1.54%	< 2%
Inter-Day Precision (% RSD)	0.16-0.69%	< 2%
Linearity range	35-2.18 µg/mL	NA
Regression equation	y = 35620x - 16027	NA
Correlation Coefficient (r2)	0.9991	NA
SE of intercept (Se)	10879.75477	NA
SD of intercept (Sa)	24327.87124	NA
LOQ[a] (µg/mL)	6.83 µg/mL	NA
LOD[a] (µg/mL)	2.05 µg/mL	NA

System Suitability: The %RSD was found to be less than 2%, indicating acceptable system performance. Table No 12 System sutability

Precision: Precision of the developed HPLC method was evaluated in terms of intraday and interday (intermediate) precision. demonstrate that the proposed method is precise for Bilastine.

Table No.13: Intraday precision data of Bilastine

Drug Name: Bilastine					
S. No.	**Concentration (ppm)**	**Area**	**Average**	**Std. Deviation**	**%RSD**
1	100 ppm	3943199	4013001	61930.48	1.54%
	100 ppm	4061361			
	100 ppm	4034443			
2	100 ppm	4038812	4055931	33847.13	0.83%
	100 ppm	4034063			
	100 ppm	4094918			
3	100 ppm	3867929	3838195	26317.75	0.69%
	100 ppm	3828765			
	100 ppm	3817892			
	Range of % RSD				0.83-1.54%

Table No.14: Interday/intermediate precision data of Bilastine

Drug Name: Bilastine					
S. No.	**Concentration (ppm)**	**Area**	**Average**	**Std. Deviation**	**%RSD**
DAY 1	100 ppm	3867929	3838195	26317.75	0.69
	100 ppm	3828765			
	100 ppm	3817892			
DAY 2	100 ppm	3815289	3820409	6010.12	0.16
	100 ppm	3818911			
	100 ppm	3827026			
DAY 3	100 ppm	3843541	3841038	7058.19	0.18
	100 ppm	3846503			
	100 ppm	3833069			
	Range of % RSD				0.16-0.69%

Robustness studies: Deliberate variations in flow rate, mobile phase composition, and detection wavelength produced only minor changes in retention time of Bilastine without significantly affecting chromatographic performance.

Table No. 15: Robustness data of Bilastine

Variables of robustness	**Bilastine**			
	Retention time t_R (min)	**Ret. factor (k')**	**Tailing factor (T_f)**	**Th. Plates (N)**
Flow rate (1.1 ml/min)	8.26	3	1.34	32332
Flow rate (0.9 ml/min)	8.82	2.41	1.21	48429
Solvent B composition (72%)	8.86	2.89	1.35	32021
Solvent B	8.5	2.74	1.32	34997

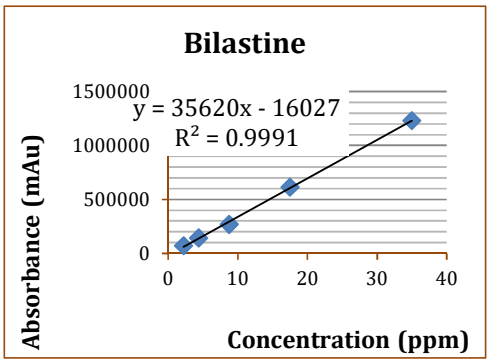
composition (68%)				
Temperature (30*C)	8.72	2.91	1.4	32719
Temperature (26*C)	8.72	2.91	1.4	32719
Average	8.65	2.81	1.34	2455.5
Standard deviation	±0.23	±0.21	±0.07	±34.62

Calibration (Linearity) studies: A strong correlation ($R^2 \approx 0.999$) was found in the linearity study of Bilastine, indicating excellent proportionality between response and concentration.

Table No.16: Linearity data of Bilastine

Name of Drug; Bilastine		
S. No.	Concentration (µg/mL)	Area
1	35 µg/mL	1231507
2	17.5 µg/mL	615172
3	8.75 µg/mL	271689
4	4.375 µg/mL	144131
5	2.1875 µg/mL	72836
Regression Equation		y = 35620x - 16027
Correlation coefficient (R^2)		0.9991
Std. error of intercept		10879.75477
Std. Dev. Of intercept		24327.87124
LOQ		6.83 µg/mL
LOD		2.05 µg/mL

Fig No.11: Calibration curve of Bilastine



Drug accuracy studies: At 80%, 100%, and 120% levels, the accuracy study of Bilastine revealed a recovery percentage of 94.02 ± 1.07%. The method is accurate and dependable, and the results fell within the ICH limits (90–110% and %RSD < 2%).

Table No.17: Accuracy data of Bilastine

Drug Name: Bilastine			**Drug content: 20 mg**		**Marketed formulation: Bilastine**		
Std. conc. (%)	**Std. (ppm)**	**Peak area**	**Drug (%)**	**Drug (ppm)**	**Peak area**	**Avg. peak area**	**Drug Rec. (%)**
100%	100 ppm	3892313	80	20	727544	727675.5	93.48%
				20	727807		
			100	25	921073	908184.5	93.33%
				25	895296		
			120	30	1122369	1112224.5	95.25%
				30	1102080		
			Drug recovery Range (%) as per ICH = 100±10%				94.02±1.07%
			Standard Deviation				1.07
			Relative Standard Deviation (RSD)				1.14%

CONCLUSION:

The study successfully demonstrated the formulation and evaluation of a Bilastine pulsatile drug delivery system suitable for chronotherapeutic applications. The developed press-coated tablets

effectively achieved a programmable lag time followed by rapid drug release, aligning with the circadian pattern of allergic symptoms. This approach enhances therapeutic efficacy and patient compliance by delivering the drug at the required time. Preformulation and evaluation studies confirmed that the selected excipients and formulation strategy were appropriate, producing tablets with acceptable physical and mechanical properties. The optimized HPLC method proved to be simple, accurate, precise, and robust, making it suitable for routine analysis of Bilastine in pharmaceutical formulations. Overall, the study concludes that the pulsatile drug delivery system of Bilastine is a promising approach for time-dependent drug delivery, particularly for the effective management of allergic conditions exhibiting circadian variation.

ACKNOWLEDGEMENT:

The authors are thankful to the Department of Quality Assurance, Vidyabharti College of Pharmacy, Amravati, Maharashtra, India, for providing the necessary facilities and support to carry out the research work. The authors also express sincere gratitude to the guide and faculty members for their valuable guidance and encouragement throughout the study.

None

CONFLICT OF INTREST:

REFERENCES:

1. Davis SS, Illum L. Int J Pharm. 1998;176:1–8.
2. Youan BC. J Control Release. 2002;98:337–53.
3. Maroni A, Zema L, Cerea M, Sangalli ME. Oral pulsatile drug delivery systems. Expert Opin Drug Deliv. 2005;2(5):855–71.
4. Pozzi F, Furlani P, Gazzaniga A, Davis SS, Wilding IR. The Time Clock system: a new oral dosage form for fast and complete release of drug after a predetermined lag time. J Control Release. 1994;31(1):99–108.
5. Smolensky MH, Peppas NA. Chronobiology, drug delivery, and chronotherapeutics. Adv Drug Deliv Rev. 2007;59(9-10):828–51.
6. Sharma S, Sharma AD, Khar RK. Pulsatile drug delivery system: a review on advanced approach. Int J Pharm Technol. 2011;3(1):1179–88.
7. United States Pharmacopeial Convention. United States Pharmacopeia 31–National Formulary 26 (USP 31–NF 26). Rockville (MD): United States Pharmacopeial Convention; 2008.
8. Yogananda Kumar G, Srinivasa Rao J, Chaitanya P. Design and in vitro evaluation of sustained release matrix tablets of potassium using HPMC polymers. Int J Pharm Sci Technol. 2011;3(1):32–44.
9. Kumar D, Jain DK. Formulation and evaluation of sustained release matrix tablets. Bull Pharm Res. 2014;4(1):1–8.
10. Udayakumar T, Suresh AG, Ubaidulla D. Formulation and evaluation of immediate and sustained release bilayered tablets of glibenclamide and metformin HCl. Int J Res Dev Pharm Sci. 2011;2:337–41.
11. Shashidhar P, Vidyasagar G, Srikanth G. Design and evaluation of metformin hydrochloride and glimepiride bilayered tablets. Int J Pharm Pharm Sci. 2011;3:78–92.
12. Collett JH, Moreton RC. Modified-release per oral dosage forms. In: Aulton ME, editor. Pharmaceutics: The Science of Dosage Form Design. London: Churchill Livingstone; 2002. p. 289–304.
13. Lachman L, Lieberman HA, Kanig JL. The Theory and Practice of Industrial Pharmacy. 3rd ed. Mumbai: Varghese Publishing House; 1991. p. 296–302.
14. International Council for Harmonisation. ICH Q2(R1): Validation of Analytical Procedures: Text and Methodology. Geneva: ICH; 2005.
15. United States Pharmacopeia. USP <1225> Validation of Compendial Procedures. Rockville (MD): United States Pharmacopeial Convention.