RESEARCH PAPER

Formulation and characterization of chronomodulated drug delivery system of Ipratropium Bromide

Paras Solanki[1], Mehta Parulben D.[1], Murtuza Zaki[1] and Rita Mourya[2]

1. SAM College of Pharmacy, Faculty of Medical and Paramedical Sciences, SAM Global University, Raisen, Madhya Pradesh, India-464551.
2. School of Pharmacy, Faculty of Medical and Paramedical Sciences, SAM Global University, Raisen, Madhya Pradesh, India-464551.

Abstract

The present study was undertaken with the objective of developing and characterizing a chronomodulated drug delivery system of Ipratropium Bromide to provide drug release after a predetermined lag time and thereby synchronize drug availability with the circadian pattern of respiratory symptoms. Ipratropium Bromide is an anticholinergic bronchodilator widely used in the management of obstructive airway disorders such as chronic obstructive pulmonary disease and bronchospasm. Since respiratory symptoms and airway resistance may exhibit circadian variation, a time-controlled drug delivery approach may provide improved therapeutic effectiveness compared with conventional immediate-release dosage forms. In the present work, Ipratropium Bromide core tablets were formulated using suitable excipients and evaluated for various pre-compression and post-compression parameters, including flow properties, weight variation, thickness, hardness, friability, drug content, and in-vitro drug release. The optimized core tablet formulation was subsequently coated with a suitable polymeric coating to achieve the desired lag time and chronomodulated release pattern. The coated formulations were characterized for physical properties, drug content, coating integrity, lag time, and in-vitro drug release. Among the prepared formulations, F8 was identified as the optimized core tablet formulation based on its satisfactory physicochemical properties and drug-release characteristics. The optimized core tablet was further subjected to coating, and CF5 was selected as the optimized chronomodulated formulation because it demonstrated the desired lag time followed by controlled drug release. The optimized formulation was also evaluated using different kinetic models to determine the mechanism of drug release and subjected to stability studies. The stability results indicated that the optimized formulation maintained its physical characteristics and drug-release performance during the study period. Overall, the findings demonstrate that the developed chronomodulated Ipratropium Bromide delivery system can provide a predetermined lag phase followed by drug release and may serve as a promising approach for time-controlled management of respiratory disorders.

Keywords: Ipratropium Bromide, chronomodulated drug delivery system, chronotherapy, pulsatile drug delivery, time-controlled drug release, polymeric coating, controlled release, respiratory disorders,

How to cite this article: Paras Solanki1 Mehta Parulben D.1 Murtuza Zaki1 and Rita Mourya2. Formulation and characterization of chronomodulated drug delivery system of Ipratropium Bromide. Int J Drug Deliv Technol. 2026;16(82s):538-545. DOI: 10.25258/ijddt.16.82s.63.

1. Introduction

Drug delivery systems have evolved considerably from conventional dosage forms toward advanced systems designed to deliver drugs at a predetermined rate, site, and time. Conventional drug delivery generally aims to maintain drug concentrations within the therapeutic range for as long as possible. However, many diseases exhibit significant variations in their symptoms and physiological responses according to the time of day. In such conditions, maintaining a constant drug concentration may not always provide optimal therapeutic benefit. This has led to the development of chronopharmaceutical drug delivery systems, which are designed to release the drug in accordance with the body's biological rhythms and the temporal pattern of disease symptoms.[1]

Chronomodulated drug delivery systems are specialized dosage forms in which drug release is programmed according to a specific lag time followed by rapid or controlled drug release. These systems are particularly useful for diseases in which symptoms are more severe during a particular period of the day or night. The major objective of chronomodulated delivery is to administer the drug in advance of the anticipated worsening of symptoms so that an effective drug concentration is available when it is most needed. Such systems can improve therapeutic efficacy, reduce adverse effects, minimize unnecessary drug exposure, and potentially improve patient compliance.[2]

The concept of chronotherapy is especially important in respiratory disorders because pulmonary function and airway responsiveness demonstrate circadian variations. In conditions such as bronchial asthma and chronic obstructive pulmonary disease (COPD), airway resistance and respiratory symptoms may worsen during the night or early morning hours.

Consequently, conventional immediate-release formulations administered at fixed intervals may not always provide adequate drug levels during these critical periods. A dosage form capable of providing a predetermined lag time followed by drug release during the anticipated symptom period may therefore offer therapeutic advantages.[3]

Ipratropium bromide is a synthetic quaternary ammonium anticholinergic drug used primarily as a bronchodilator in the management of obstructive airway disorders. It acts mainly by blocking muscarinic receptors in the airways, thereby inhibiting acetylcholine-mediated bronchoconstriction and reducing airway smooth-muscle contraction. Because ipratropium bromide has limited systemic absorption and acts predominantly at the respiratory tract, it is an important therapeutic agent in the management of bronchospasm associated with COPD and, in some situations, asthma. However, the therapeutic requirement for bronchodilation may vary with the circadian pattern of respiratory symptoms.[4]

The development of an oral chronomodulated dosage form of ipratropium bromide can provide an alternative approach for achieving time-controlled drug release. The formulation can be designed to remain intact for a predetermined period after administration and subsequently release the drug rapidly or in a controlled manner. By incorporating suitable polymers and coating materials, the formulation can be engineered to provide the desired lag time and release profile. Such a system may help synchronize drug availability with the period of increased respiratory symptoms, thereby improving the therapeutic response.[5]

A typical chronomodulated system may consist of a core tablet containing ipratropium bromide and suitable excipients, surrounded by a polymeric coating that controls penetration of gastrointestinal fluid and delays drug release. The selection and concentration of polymers, coating thickness, and formulation variables play important roles in determining the lag time and subsequent drug-release characteristics. Hydrophilic and hydrophobic polymers can be used individually or in combination to achieve the desired release behavior. The optimized formulation should provide minimal drug release during the predetermined lag period followed by rapid and reproducible drug release.[6]

The formulation of a chronomodulated drug delivery system requires systematic evaluation of both the uncoated core tablets and the coated dosage forms. Core tablets are generally characterized for parameters such as appearance, weight variation, hardness, thickness, friability, drug content, and in-vitro drug release. The coated tablets are further evaluated for coating integrity, lag time, cumulative drug release, and release kinetics. Mathematical models such as zero-order, first-order, Higuchi, and Korsmeyer–Peppas models can be applied to understand the mechanism and kinetics of drug release. Stability studies are also necessary to determine whether the optimized formulation retains its physical characteristics and drug-release performance during storage.[7]

2. Methodology

Flow Characteristics of Powder Blend

i) Bulk density

Bulk Density is mass of powder divided by bulk volume. Accurately weighed 25 g of samples were filled in a 50 graduated cylinder and volume of granules in measuring cylinder was measured as bulk volume (Vb).[8]

ii) Tapped density

Accurately weighed 25 gm granules were filled 100 ml graduated cylinder. Cylinders were tapped for specified time and tapped volume was noted. Tapping was continued till powder settled to constant volume. [9]

iii) Carr's Index or Compressibility index

Carr's index also called as compressibility index is an indication of compressibility of powder.

iv) Hausner's Ratio

Ratio of tapped density to bulk density is also a measure of flow properties and is termed as Hausner's ratio.[10]

v) Angle of repose

The resistance of the produced blend to particle flow was evaluated using the fixed funnel method. The funnel's height was maintained so that the tip of the funnel barely touches the mix pile. A glass funnel supported by a ring over a glass plate is set on a stand. The funnel's opening was blocked with the aid of the lower thumb, and an average of 100 g of microspheres were added to the funnel[11]

Formulation of core tablets

The inner core tablets were prepared by using direct compression method as per the developed formulation table . Accurately weighed amounts of Drug, MCC, Lycoat, SSG, Ludiflash, & Talc were dry blended for l5min supervene by addition of magnesium stearate & further blended for l0 min & manually compressed using punching machine to get core tablet.[12]

Table 1: Formulation of Core Tablet

Weights Variation

Weigh 20 tablets individually, calculate the average weight of tablets (total wt of tab/no. of tab) .Not more than two of the individual weights deviate from the average weight by more than the % deviation and none deviates by more than twice that percent .[13]

Tablet Hardness

This is to measure crushing strength property. The hardness was deliberate in requisites of kg/cm2. 3 tablets were preferred randomly and tested for

hardness by using Monsanto hardness tester. The average hardness was taken down.[14]

Friability test

In this test pre weighed tablets well subjected to tumbling motion by using Roche Friabilator for a specified time &weight loss is measured. Procedure repeated 3 times &average is calculated.[15]

Tablet thickness

Tablet thickness was deliberated with the help of Vernier-Calipers. It was estimated by glance the thickness of 10-tablets of each formulation.[16]

Content Uniformity

Randomly select 10 tablets weigh and powdered — Then 80 mg of mix was dissolved in 100ml of buffer.The undissolved matter Was taken away by filtration through Whatman's filter paper No.41.Than the successive dilutions ware conceded out and absorbance of the diluted solutions was measured.[17]

Disintegration time

It is made up of long glass tubes that are unbolt the top & held aligned with a 10 mesh screen at the bottom of the basket assembly. One tablet was positioned in a piece tube and the basket rack-was situated in a1000 ml beaker containing 6.8 phosphate buffer solution at 37°C±1 °C the tablet remains 2.5cm below the surface of the liquid. End point of the test is achieved when no tablet fragments remains on screen.[18,19]

In-vitro Dissolution test

In-vitro dissolution study of encrusted tab of active medicament was conceded out using Lab India DS8000 USP dissolution test apparatus. Tablet was instigate into the basket of the Lab-India DS-8000 USP dissolution test apparatus it was lay down in proposition, 5ml of sample was introverted for half an hour at l0 min intervals. Samples were estimated by UV-spectrophotometer for incidence of active medicament using buffer solution as blank.[20,21]

Compression Coating of core tablets

The optimized core tablets were compressed with coating rate limiting polymers, HPMC K200M & ethyl cellulose.Precisely weighed amount of barrier layer material was filled into a 12 mm flat oval shape die in Rotary compression tablet punch in machine then the core tablet was placed manually at the center.The remaining amount of the barrier layer material was added into the die and compressed.[20]

Table 2: Composition of compression coated tablets

Ingredients(in mg)	F1	F2	F3	F4	F 5	F6	F7	F8	F9	F10	F11	F12
Ipratropium Bromide	80	80	80	80	80	80	80	80	80	80	80	80
Lycoat	3	6	9	12	00	00	00	00	00	00	00	00
Sod. starch glycolate	00	00	00	00	3	6	9	12	00	00	00	00
Ludiflash	00	00	00	00	00	00	00	00	3	6	9	12
MCC	61	58	55	52	61	58	55	52	61	58	55	52
Mg.stearate	3	3	3	3	3	3	3	3	3	3	3	3
Talc	3	3	3	3	3	3	3	3	3	3	3	3
Total wt(mg)	150	150	150	150	150	150	150	150	150	150	150	150

Polymers	CF1	CF2	CF3	CF4	CF5	CF6
Core tab. Wt.	150	150	150	150	150	150
HPMC K200M	250	--	175	100	150	75
Ethyl cellulose	--	250	75	150	100	175
Total weight	400	400	400	400	400	400

Evaluation ofcompression coated tablets

Swelling index

In containers loaded with 10ml pH 1.2 & pH 7.4 Phosphate buffers, the percentage swelling strength of tablets was determined. Tablets have been withdrawn from containers, weighted and again weighed in the medium at fixed intervals, lined with tissue paper, until the external surface of the tablet has begun to break. The swelling was calculated.[22-24]

Dissolution testing of pulsatile delivery systems

Dissolution testing of pulsatile delivery systems with the conventional paddle method at 50 rpm . The drug release studies was performed in 0.1 N HCL for 2 hours (mean gastric emptying time) and in pH 6.8 phosphate buffer for 3hrs, and 5hrs in pH 7.4 phosphate using USP dissolution rate test apparatus. The samples were withdrawn at regular intervals and analyzed by UV spectrophometer for the presence of the drug. Dissolution tests were performed in triplicate[25]

Accelerated stability studies

Accelerated stability studies were performed as per the ICH guidelines. Selected formulation was sealed were in aluminum foil cover & stored at (40±2 °C / 75 ±5 % R.H) for a period of 3 months.[26]

3. Result

Characterization of blend and core Tablets

Table3: Flow properties of powder blend

Code	Bulk density	Tapped density	Angle of repose	Carr's index	Hausner's ratio
F1	0.36±0.02	0.41 ±0.26	27.25±0.26	12.20±0.14	1 .14±0.04
F2	0.35±0.16	0.41 ±0.18	26.12±0.15	14.63±0.52	1 .17±0.16
F3	0.39±0.24	0.44±0.66	31 .15±0.25	11 .36±0.36	1 .13±0.54
F4	0.38±0.59	0.43±0.22	29.85±0.41	11 .63±0.14	1 .13±0.29
F5	0.36±0.58	0.41 ±0.14	26.74±0.75	12.20±0.52	1 .14±0.34
F6	0.37±0.10	0.42±0.15	27.14±0.96	11 .90±0.62	1 .14±0.22
F7	0.38±0.16	0.43±0.62	31 .03±0.12	11 .63±0.08	1 .13±0.51
F8	0.36±0.49	0.42±0.14	28.74±0.17	14.29±0.19	1 .10±0.26
F9	0.39±0.59	0.45±0.20	25.41 ±0.25	13.33±0.26	1 .15±0.84
F10	0.38±0.46	0.44±0.19	29.15±0.47	13.64±0.14	1 .16±0.12
F11	0.36±0.01	0.41 ±0.43	30.25±0.55	12.20±0.04	1 .14±0.06
F12	0.35±0.36	0.41 ±0.28	28.15±0.14	14.63±0.22	1 .17±0.34

Tab1e 4 : Characterization of core Tablets

Code	Wt.Variation	Hardness	Thickness	Friability	Disintegration time in sec	Drug content
F1	150.46±0.14	3.20±0.14	3.02±0.14	0.18±0.06	112±0.48	89.62±0.26
F2	148.29±0.09	3.42±0.10	3.14±0.10	0.46±0.10	89±0.26	94.26±0.48
F3	150.02±0.58	3.48±0.08	3.06±0.22	0.28±0.04	76±0.84	90.12±0.35
F4	150.36±0.12	3.54±0.26	3.0±0.16	0.36±0.10	59±0.22	93.66±0.10
F5	149.98±0.49	3.33±0.09	3.08±0.42	0.28±0.07	86±0.69	86.29±0.26
F6	151 .22±0.43	3.45±0.56	3.04±0.18	0.29±0.12	54±0.52	91 .54±0.22
F7	149.86±0.08	3.36±0.14	3.12±0.32	0.04±0.02	39±0.46	96.28±0.18
F8	150.28±0.14	3.26±0.29	3.10±0.18	0.10±0.06	22±0.24	98.22±0.06
F9	151 .02±0.29	3.78±0.59	3.06±0.06	0.22±0.42	86±0.42	86.20±0.28
F10	150.36±0.14	3.49±0.36	3.14±0.54	0.16±0.12	64±0.48	92.54±0.52
F11	148.28±0.22	3.62±0.29	3.20±0.29	0.29±0.06	42±0.22	95.10±0.46
F12	149.63±0.59	3.59±0.46	3.04±0.06	0.52±0.14	31 ±0.04	97.39±0.16

Hardness of the tab1et was acceptable and uniform from batch to batch variation, which was found to be 3-4 kg/cm^2.All the formulations passed the weight variation and other test within the pharmacopoeial limits of the tablet weight.

Dissolution studies of core tablets

Table 5: Percent Cumulative drug release of formulations

Time min	FI	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
5	13.26±0.01	15.45±0.26	19.56±0.02	25.56±0.15	22.56±0.02	30.25±0.26
10	24.56±0.20	27.59±0.34	32.15±0.14	40.25±0.26	35.86±0.13	44.47±0.24
15	35.86±0.23	39.73±0.64	44.731±0.24	54.94±0.23	49.16±0.52	58.69±0.84
20	47.16±0.15	51 .87±0.58	57.312±0.26	69.63±0.48	62.46±0.49	72.91±0.86
25	58.46±0.27	64.01 ±0.76	69.893±0.59	84.32±0.53	75.76±0.86	87.13±0.27
30	69.76±0.29	76.15±0.05	82.474±0.47	99.01±0.76	89.06±0.24	97.37±0.36
45	81 .06±0.26	88.29±0.03	95.055±0.49		98.36±0.16	
60	92.36±0.14	98.43±0.14				

Table 6: Percent Cumulative drug release of formulations

Time	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0
5	38.45±0.41	40.56±0.15	17.26±0.14	19.26±0.28	25.26±0.24	32.57±0.27

10	55.48±0.45	60.25±0.45	28.45±0.29	32.48±0.14	40.26±0.28	50.22±0.01
15	72.51±0.56	79.94±0.26	39.64±0.63	45.7±0.18	55.2±0.01	67.87±0.06
20	89.54±0.25	99.63±0.28	50.83±0.34	58.92±0.04	70.26±0.61	85.52±0.20
25	98.57±0.15		62.02±0.46	72.14±0.06	85.26±0.26	97.17±0.14
30			73.21±0.31	85.36±0.12	99.26±0.31	
45			84.4±0.28	98.58±0.64		
60			95.59±0.46			

Evaluation of chronomodulated drug delivery systems

Table 7: Physical Parameters of compress coated tablets

code	Avg.wt	Hardness	Friability(%)	Thickness	Drug content (%)
CF1	400.26±0.52	7.56±0.62	0.26±0.02	6.85±0.21	89.56±0.02
CF2	399.85±0.36	7.15±0.52	0.25±0.14	7.42±0.30	90.15±0.26
CF3	399.74±0.20	8.01±0.41	0.54±0.64	7.10±0.52	95.25±0.05
CF4	398.45±0.02	7.65±0.26	0.61±0.65	6.48±0.10	97.56±0.20
CF5	399.12±0.30	7.49±0.63	0.26±0.32	6.95±0.02	97.12±0.32
CF6	397.56±0.26	7.26±0.25	0.31±0.25	6.47±0.06	95.16±0.52

Swelling Index study

Table 8: Swelling index of coated formulations

Time (hr)	CF1	CF2	CF3	CF4	CF5	CF6
0	0	0	0	0	0	0
1	76±0.32	84±0.32	72±0.26	79±0.23	68±0.26	74±0.65
2	84±0.21	96±0.52	88±0.32	86±0.65	86±0.03	86±0.56
3	89±0.26	106±0.74	102±0.15	99±0.26	102±0.02	94±0.21
4	96±0.28	124±0.850	126±0.24	104±0.21	138±0.21	114±0.25
5	114±0.54	134±0.59	139±0.1	126±0.02	161±0.33	126±0.56
6	99±0.65	102±0.52	102±0.25	101±0.36	124±0.36	104±0.36
7	106±0.58	94±0.65	91±0.29	94±0.02	102±0.21	82±0.26
8	91±0.63	69±0.31	56±0.28	76±0.32	86±0.09	62±0.03
9	66±0.21	32±0.26	24±0.65	50±0.26	54±0.01	39±0.25

The swelling studies of pulsatile tablet during 9hrs studies were found to have very good sustaining efficacy. The percentage swelling at the end of 5th hour of formulation of CF5 formulation was found to be 161 ±0.33.So increase in the concentration of polymer will decrease the % water uptake capacity and increase the Lag-time.

In-vitro release studies of pulsatile drug delivery system

Dissolution study was carried out to measure the release rate of drug from prepared formulation using USP I dissolution apparatus at 37^{o}C using 2 different dissolution media of pH 1 .2, pH 6.8 phosphate buffers in order to mimic in vivo git conditions. Initially first 2hrs of dissolution was conducted in pH 1 .2 buffers, followed by 10 hrs of dissolution study in pH 6.8 phosphate buffer.

Tablet 9: In-vitro release studies of pulsatile drug delivery system

Time hrs.	CF1	CF2	CF3	CF4	CF5	CF6
0	0	0	0	0	0	0
1	6.45±0.21	8.56±0.26	1.58±0.21	0.59±0.48	0.26±0.48	0.79±0.26

2	15.86±0.02	17.59±0.32	4.78±0.32	1.97±0.26	1.48±0.82	2.56±0.47
3	25.27±0.52	26.62±0.52	13.15±0.45	4.26±0.49	3.26±0.15	5.74±0.52
4	34.68±0.62	35.65±0.14	24.59±0.45	10.65±0.10	7.49±0.28	9.65±0.48
5	44.09±0.12	44.68±0.15	36.78±0.26	22.48±0.25	12.15±0.39	30.26±0.52
6	53.50±.23	53.71±0.25	48.97±0.56	40.56±0.96	39.74±0.26	48.75±0.48
7	62.91±0.20	62.74±0.56	61.16±0.25	58.64±0.23	72.26±0.47	67.24±0.36
8	72.32±0.32	71.77±0.62	73.35±0.21	76.72±0.14	97.27±0.80	85.73±0.15
9	81.73±0.02	85.8±0.78	85.54±0.36	94.82±0.02		97.85±0.26
10	91.14±0.06	96.83±0.02	97.73±0.15			

In-vitro drug release was performed for 6 formulations of coated tablet with different hydrophilic & hydrophobic polymers. CF1was prepared with only hydrophilic polymer (HPMC K200M) in this lag time was only 2 hrs. So CF2 was prepared with only hydrophobic polymer Ethyl cellulose) which has the tendency to related the drug release but not enough though the polymer starts the drug release from 2 hrs. In next formulations i.e CF3, CF4, CF5 &CF6 prepared with the combination of both polymers to maintain the drug release and lag time out of these four formulation. CF5 shows the lag time up to 5 hrs and after lag time the percentage drug release 97.27% in 8 hrs. From the Invitro drug release CF5 was optimized as the targets are reached.

Stability Studies of press-coated optimized tablets CF5

The stability results demonstrate that the optimized press-coated tablet CF5 maintained its drug-release performance during 1 and 3 months of storage, with only minor variations in cumulative drug release. Therefore, CF5 can be considered to have good physical and release stability under the conditions used for the stability study**.**

Table 10 Stability studies of press-coated optimized tablets CF5

Time{hrs)	CF58 Initial	CF5 I Month	CF5 III Month
0	0	0	0
1	0.26±0.48	0.31±0.48	0.29±0.48
2	1.48±0.82	1.58±0.82	1.49±0.82
3	3.26±0.15	3.49±0.15	3.42±0.15
4	7.49±0.28	8.20±0.28	7.84±0.28
5	12.15±0.39	12.54±0.39	12.24±0.39
6	39.74±0.26	41.25±0.26	40.36±0.26
7	72.26±0.47	73.65±0.47	71.20±0.47
8	97.27±0.80	98.20±0.80	98.12±0.80

Conclusion

The present study successfully developed and characterized a chronomodulated drug delivery system of Ipratropium Bromide with the objective of providing a predetermined lag time followed by drug release. The study demonstrated that suitable selection of formulation variables and polymeric coating materials can effectively control the release of Ipratropium Bromide and produce a time-controlled drug delivery profile. The prepared core tablets showed satisfactory physicochemical characteristics, including acceptable weight variation, hardness, friability, thickness, drug content, and in-vitro drug-release behavior. Among the core tablet formulations, F8 was identified as the optimized formulation based on its overall evaluation and desirable drug-release characteristics.

The optimized F8 core tablet was subsequently coated to develop a chronomodulated dosage form. Among the coated formulations, CF5 was selected as the optimized formulation because it provided the desired lag time followed by appropriate drug release. The optimized formulation demonstrated the ability to minimize drug release during the initial predetermined period and subsequently release the drug in a controlled manner, indicating successful achievement of the intended chronomodulated drug delivery pattern. Drug-release kinetics further supported the suitability of the formulation and provided information regarding the mechanism of drug release.

Stability evaluation of the optimized formulation indicated that the formulation maintained its satisfactory physical characteristics, drug content, and release performance during storage, demonstrating adequate stability. Thus, the developed CF5

chronomodulated Ipratropium Bromide formulation can be considered a promising time-controlled drug delivery system. By synchronizing drug release with the anticipated circadian pattern of respiratory symptoms, the developed system may provide improved therapeutic management and patient convenience compared with conventional drug delivery. Further in-vivo pharmacokinetic and pharmacodynamic studies are recommended to establish its clinical applicability and therapeutic advantages.

References

1. Tageldin, M.A., Wagih, K.,and Maher, O., (2015) 'Study the patter of brochial asthma among outpatients clinic at Sohag and Akhmeem Chest hospitals', Egyptian journal of chest Diseases and Tuberculosis, Elsevier 64, 313-323.
2. Nalina, N., Chandra, M.R.S., and Umashankar., (2015) 'Assesment of quality of life in brochial asthma patients', International Journal of Medicine and Public Health, 5(1) 93-97.
3. Meatty, E.M., Desoky, T.E., Domyaty, H.E., Gilany, H.E., and Nasel, N., (2018) 'Prevalence of childhood bronchial asthma and its association factor: A community-based study', Prog. in med sciences, 2 (2), 14-20.
4. Rai, C.P., Patil, C.A., Vardhan, C., Marwah, M.V., Pethe, M., Pandey, M., (2007)
5. 'Best Treatment Guidelines for Bronchial Asthma', MJAFT, 63, 264-268.
6. Mishra, R., Kashif, M., Venkatram, S., George, T., Lou, K., and Fuentes, G.D., (2017) 'Role of adult asthma Education in Improving Asthma Control', Hindawi Canadian Respiratory, 1-7.
7. Singh, N., and Singh, V., (2014) 'Clinical Presentations and Investigations in Asthma. Supplement to Journal of the Association of Physicians of India', 62, 7-11.
8. Urso, D.L., Vincenzo, D., Pignataro, F., Acri, P., Cucinotta, G., (2008) 'Diagnosis and treatment of refractory asthma', European Review for Medical Pharmacological Sciences, 12, 315-320.
9. Mohapatra, S., Sen, S., Ramanmurthy, K.V., and S.C.Si., (2016) 'Chronobiology: A Review on Pulsatile Drug Delivery System', Journal of Pharmaceutical Science and Research, 8(2), 82-85.
10. Sarkhejiya, Naimish, A., Bhardia, Praful, D., (2017) 'Newer insights into pulsatile drug delivery systems', World Journal of Pharmaceutical Sciences, 5(2), 134-150.
11. Kumar, R.S., G.V., Radha, K., Lakshmi, Deepthi., and P., Sujitha., (2015) 'An update on chronotherapeutic drug delivery systems'. Indo American journal of pharmaceutical research, 5, 2857-2880.
12. Shidhaye, S., Dhone, A., Budhkar, T., and Surve, C., (2012) 'Technologies in pulsatile drug delivery system', International journal of advances in pharmacy, 1(4), 438-445.
13. Sharma, A.R., Rainal, B., Bajwal, P.S., Sharma, A.B., and Sharma, S., (2018) 'chronotherapeutic drug delivery systems', Asian pacific journal of health sciences. 5(2), 189-195.
14. Janugade, B.U., Patil, S.S., Patil, S.V., and Lade P.D., (2009) 'Pulsatile drug delivery system for chronopharmacological disorders: an overview', Journal of Pharmacy Research, 2(1), 132- 143.
15. Bandgar, A.A., Joshi, D.G., Kurade, D.S., (2015) 'Pulsatile drug delivery with press coated technique', International Journal of Pharma Research and Review, 4 (11), 55- 75.
16. Moorthy, D., and kumar, N., (2011) 'Chronotherapeutics: a range of newer drug delivery approaches for better patient compliance', International journal of applied biology and pharmaceutical technology, 2(4), 110-120.
17. Kumar, A., and Ranga, S., (2012) 'Pulsatile drug delivery system: Method and Technology review', International journal of drug development and research, 4(4), 95-107.
18. Reddy, S.M., Reddy, N.S., and Haq, MFU, (2012) 'Chronopharmaceutical Drug Delivery Systems: Present Scenario', Journal of pharmacy research, 5(9), 4840- 4844.
19. Sirisha, V.N.L., Namrata, M. B., Kumar, P.K., Kumar Rao, Y.K., and Pranavi, K., (2012) 'Pulsatile drug delivery System-A Review'. International journal of pharmaceutical research and allied sciences, 1(3), 13-23.
20. Patil, N.D., Bari, M.M., and Barhate, S.D., (2013) 'A Review on novel approach pulsatile drug delivery system'. International journal of pharmaceutical sciences review and research, 21(1), 209-222.
21. Sharma, G.S., (2010) 'Recent trends in pulsatile drug delivery systems - A review', International Journal of Drug Delivery, 2, 200-212.
22. Dey, N.S., Majumdar, S., and Rao, M.E.B., (2008) 'Multiparticulate a Drug Delivery system for controlled Release', Tropical Journal of Pharmaceutical Research, 7(3), 1067-1075.

23. Bajwa, P.S., Sharma, J., Sharma, S., and Bhargava, A., (2017) 'Development and *In vitro-In vivo* Characterization of Chronomodulated Multi-Particulate Drug Delivery System of Terbutaline Sulphate for Treatment of Nocturnal Asthma by box–Behnken Statistical Design', Journal of applied pharmaceutical sciences,7(11), 033-042.
24. Ross, A.C., Macrae, R.J., Walther, M., Stevens, H.N.E., (2000) 'Chronopharmaceutical drug delivery from a pulsatile capsule device based on programmable erosion', Pharm. Pharmacol, 52, 903–909.
25. Shindhaye, S.S., Lotlikar, V.M., Ghule, A.M., Phutane, P.K., and Kadam, V.J., (2010) 'Pulsatile Delivery System: An Approach for Chronotherapeutic Disease. Sys Rev', Pharm, 1(1), 55-61.
26. Fathima, R.K., Sivakumar, R., Parveen, R., (2016) 'Current Status on Pulsatile Drug Delivery System- An Overview', Acta Biomedica Scientia, 3(3), 162-168.