International Journal of Applied Pharmaceutics

ISSN- 0975-7058 Vol 14, Issue 4, 2022

Review Article

CIRCADIAN RHYTHMS REGULATED ASTHMA TREATMENT BY VIRTUE OF PULSATILE DRUG DELIVERY SYSTEM

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Received: 11 Feb 2022, Revised and Accepted: 15 Apr 2022

ABSTRACT

Asthma, as we all know, is a disease that shows a high tendency of chronic inflammation in the airways, which associates with airflow obstruction. Lung function seems to be decreased in the case of people suffering from asthma. On reviewing many studies from the past, clear statements come out which also revealed that asthma is based on established circadian rhythm. Asthma is considered to be one of the diseases which affects majorly common in adult women than in men; according to numerous studies, 42 percent of persons with active asthma claimed that their asthma started before they were 16 y old. The pulsatile drug delivery system, an innovation in pharmaceutical technology, is generating huge attention these days and is alleged to be the most productive in the treatment of asthma as per many studies. Many pulsatile delivery system components, such as the osmotic system, capsular system, and single and multiple-unit system, are utilized to diagnose and treat diseases caused by biological rhythm disturbances. Various emerging diseases such as cardiovascular, peptic ulcer, asthma, peptic ulcer, diabetes mellitus, cancer, and hypercholesterolemia have been examined by fluctuation in biological rhythms and treated by a pulsatile drug delivery system. During this era, the pulsatile drug delivery system delivers the medicine at the right time duration, in the right place, and the right proportion and the effectiveness of pulsatile drug delivery on asthma have indeed been investigated in this article.

Keywords: Asthma**,** Pulsatile drug delivery system (PDDS), Circadian rhythm, Chronotherapeutic

DOI: https://dx.doi.org/10.22159/ijap.2022v14i4.44395. Journal homepage: https://innovareacademics.in/journals/index.php/ijap

INTRODUCTION

Asthma is a disorder that influences a huge number of youngsters these days. Asthma affects one in every six adults and a quarter of all children, according to the World Health Organization (WHO) [1]. It is usually at its highest at about 4 p. m. and lowest around 4 a. m. Asthma symptoms evolve, leading to fluctuations in airway inflammation and physiology, so the motive is to understand how biological rhythms work on a time to time basis so that there will be a clear affirmation that circadian rhythm is important in the pathogenesis of asthma [2]. Lower airway secretions, as well as cortisol, vagal tone, and body temperature, may be affected by circadian rhythm in epinephrine, AMP, histamine, and other inflammatory mediators, cortisol, vagal tone, and body temperature [3]. The goal is to have a 6 hour lag time i.e. the medication taken before going to bed and is supposed to release the medicine after 6 h i.e. at 4 a. m. when asthma attacks are more common. Sigmoidal release profiles characterize chronotherapeutic medicines, with a period of no release (lag time) followed by a rapid and full release of the medication [4]. Drug-containing cores are mostly used to provide such time-controlled pulsatile administration in the treatment. The pulsatile drug delivery system is the field that is the most suitable for asthma treatment through which we can achieve optimized outcomes and minimum side effects by providing medication or drug at the right time and right efficacy [5]. In a time-controlled Pulsatile drug delivery system (PDDS), the drug release is primarily controlled by the delivery system; stimuli induced PDDS, in which release is controlled by stimuli such as temperature, pH, or enzymes present in the intestinal tract whereas in externally regulated systems, the release of drug is programmed by external stimuli such as magnetism, ultrasound, electrical effect, and irradiation which are considered as external factors [6].

When it comes terms of pharmacokinetic parameters, the route of delivery varies in terms of onset of action. In the case of asthma treatment where it is proven that fast onset of action is required; the most preferable treatment is through a pulsatile drug delivery system in terms of traditional drug deliveries [7]. When we compare the pattern of oral medication with pulsatile drug delivery, the oral drug delivery Follows a predictable pattern of release and its therapeutic concentration throughout the treatment, but pulsatile drug delivery makes the treatment so easier and beneficial in every aspect because the drug is quick and speedy release in a minute or short amount of time followed by its delayed action [8]. To put it in another way, the drug must not be released during its first phase of administration, it must show its pharmacokinetic parameter where it tends to show and it is only possible to use pulsatile drug delivery because of its unique pattern and characterization after a lag period which is achieved by using different polymer and other active ingredients in the formulation of pulsatile drug delivery [9].

In today's era, what part does the pulsatile drug delivery system play?

In the present era, it is found that pulsatile drug delivery is one device that seeks to release pharmaceuticals according to a predetermined schedule, such as at the right time and the right place of action. It is currently gaining popularity because it provides a more complex alternative to standard sustained drug administration, such as a constant amount of drug released per unit time or constant blood levels [10]. A novel technique PDDS is designed in such a way that it disintegrates in a very fast way so the action of the drug will be rapid and effective. Different kinds of excipient and polymer are used to make the drug suitable for PDDS. The polymer layer and the super disintegrants used in PDDS make the drug target a specific area at the right time and the surplus amount of drug shows its optimum action. The PDDS usually contains an inert core with the main API or the drug, which consists of super disintegrants which allow the drug to disintegrate fast and the outer layer is coated with a suitable polymer with a different type of coating methods [11]. The selection of polymer is based on the type of nature of the drug i.e. different compositions of hydrophilic and hydrophobic polymer. The coating polymer should be selected adequately and quantified in such a way that it should meet lag time expectations and drug release profile in the intestine and gastric region. The release pattern is the uttermost important parameter through which the right efficacy, the right onset of action, and the right timing have been achieved and it is only possible after a drug attains a certain period of lag time before its release and is shown in (fig. 1) [12].

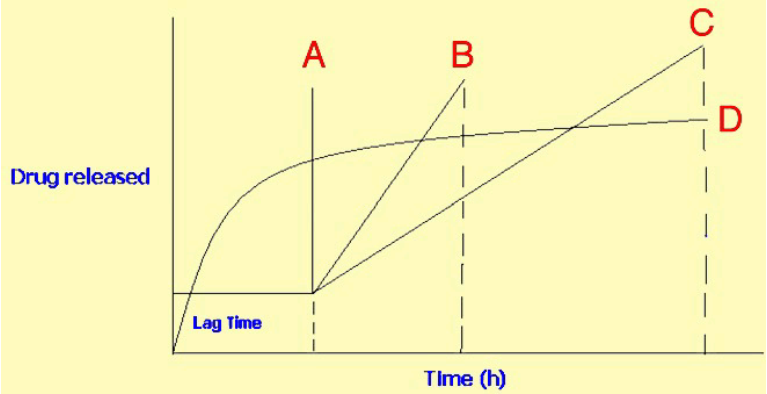

Fig. 1: A. Represent pulsatile drug release pattern after an interval of lag time [30], B. Retard Release after a certain lag period. C. Continued release after a lag time. D. Prolong release without the involvement of lag time

Pdds advantages

- Getting targeted delivery to the colon is simple [13].
- The drug's adaptability to the disease [14].
- The reduction in the dose frequency, doze size, and cost tends to reduce the side effects; thereby it
- Also helps in patient acceptability [15].
- Because fewer dosage units are required by the patient in therapy, the daily cost to the patient is lower.
- Mucosa protection from irritant medicines.
- Drugs are not lost due to large first-pass metabolism [16].

Pdds restrictions

- There is a lack of manufacturing reproducibility and efficiency.
- Technology formulations are more expensive.
- Personnel who are well-trained and skilled in the manufacturing industry [17].

The various diseases and disorders show some chronological behavior in terms of circadian rhythm and according to their disease pattern, various Chrono therapeutics or pulsatile drugs have been achieved for the most effective treatment, as shown in table 1.

Table 1: List of diseases, as well as their chronological behavior and the drugs used to treat them

Diseases	Chronological etiquette	Drug practiced	References
Asthma	The lungs' tiny airways are inflamed and Congested. The most usual periods for attacks Are late at night or early in the morning.	Theophylline, Beta, Agonist, Antihistaminic, Corticosteroids	[18]
Arthritis	C-reactive protein (CRP) is a marker of Inflammation. The levels of c-reactive protein (CRP) and interleukin-6(il-6) in the blood have Increased. Early in the morning, severe pain Occurs.	NSAIDS Counter Irritants, Corticosteroids, (DMARDs)	[19]
Cardiac Disease/ Hypertension	Blood pressure rises quickly in the morning. Steadily decreases in the evening and reaches Its lowest point is during sleep.	Anti-Thrombotic, Nitro-Glycerin, Beta Blockers, Calcium Channel Blockers	[20]
Diabetes Mellitus	Urination on a frequent basis, as well as an Abnormally high concentration of sugar in the Circulation after a meal, are both signs of Diabetes.	Sulfonylurea Alpha Glucosidase, Insulin	[21]
Ulcer	It's possible to get sores on the stomach, lower Oesophagus, or small intestine lining. Acid Secretion rises at night and throughout the day.	Proton Pump Blocker Antacids, Anti-Diarrhoeal	[22]
Hyper Cholesterol	The sum of cholestrin produced at night is more Than that produced during the daytime.	Statins Beta Blockers	[23]
Cancer	During daily activity periods, tumor blood Glide is three times higher than during dailyRest phases.	Vinca Alkaloids, Taxanes, Alkylating Agents, Anti-Tumor Drugs	[24]

Methodologies for pulsatile drug delivery system

The techniques for pulsatile drug delivery are categorized into 3 classes:

- Time is regulated.
- Induced using external stimuli
- Regulated externally

Pulsatile release system with a time control

According to new research, diseases follow probable cyclic patterns, and that scheduling treatment routine can improve outcomes in certain chronic illnesses. Consequently, novel drug delivery methods must be devised to mimic the function of biological systems while minimizing the risk of undesired side effects [25]. After a certain amount of time, a time-controlled drug delivery system can fool the circadian cycle. Besides the medication, the core also contains an immobile osmotic agent and adequate disintegrants. Semi-permeable membranes may be used as rate controllers for water entry into the osmotic core once a protective layer has been placed on individual units. The osmotic pressure in the core increases as water enters. The drug is quickly released when the core bursts [26, 27].

A delivery system containing a rupturable coating layer

While ordinarily impermeable to the rupturing event that happens automatically, this device features an outside launch control that is water-insoluble. Over time, the reservoir core is eroded or damaged, allowing the medicine to be released. With an outward enteric coating alternatively coated with HPMC and a reservoir-type device such as the chronotropic system, the lag time before drug release may be altered by the thickness of the coating layer. Drug liberation lag time is determined by HPMC density and viscosity class, as demonstrated in (fig. 2) [27–30].

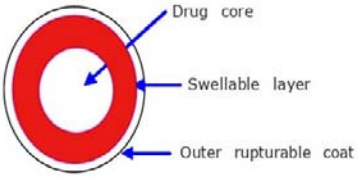

Fig. 2: Delivery system containing rupturable coating layer [30]

Delivery system with an erodible coating layer

Bulk eroding system

Certain bulk eroding polymers are available in which one of these is poly (lactide-co-glycolide), where the entrance is faster than the rate of disintegration. Degradation occurs all over the polymer sample until it reaches a specified molecular weight, at which point the point of degradation becomes little enough to be easily solubilized. At a certain point, the structure becomes more hydrated and porous so it will be possible for the drug dissolved in the polymer matrix to get released As a result, occurrences of lag time will take place before the drug gets liberated, which coincides with the time it takes for the critical molecular weight to be attained [32–34].

Surface eroding system

Surface tension degrades a wide variety of polymers, including poly anhydrides and polyester. This suggests that the breakdown of the polymer occurs at such a pace that mass loss occurs quicker than water entry. So it says that the sample present is eroded off the surface at a certain pace. During the eroding process, the polymer releases its medication at a steady pace, as seen in (fig. 3) [35].

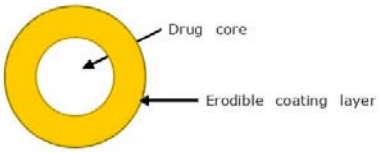

Fig. 3: Delivery system with erodible coating layer [30]

Capsular drug delivery based on expandable orifice

Both a lengthy release period and a high bioavailability may be achieved using this approach. Liquid dosage forms are advantageous for hydrophilic medications, polypeptides, and polysaccharides. The technique uses osmotic infusion to provide the drug. As the osmosis process advances, the wall expands as a result of the increased pressure within the system. Increasing the flexible wall's value causes the hole to widen, allowing for the proper rate of medicine delivery [36].

Stimuli induced pulsatile drug delivery

This kind of drug delivery includes the involvement of biological factors like thermal activities and other chemical stimulant. This consists of further classification described below. Temperature-induced systems and chemical-stimuli-induced systems are two subcategories of these systems. Drug distribution relies heavily on the external environment, as shown in (fig. 4) [37].

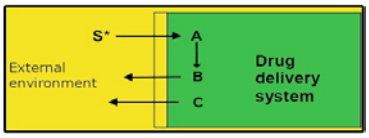

Fig. 4: Stimuli induced pulsatile drug delivery [30], S*= Outer stimuli, A = Internal substrate activation by the stimuli Presence, B= Product formed after stimuli changes, C = Drug

Thermal induced or temperature-induced system

Different polymer properties are used in temperature-induced frameworks, such as thermally reversible curl/globule progression of polymer particles increasing differences in systems, glass transition, and transparent liquefying [39]. In this type of system, the temperature is most crucial for drug liberation or release. There will be a rise in the temperature of the human body (37 degrees) where there will be the presence of pyrogens. Other than these for example, hydrogels, thermal differences cause reversible interchange in them. A transition temperature at which the gel's lower critical solution temperature is reached causes the gel to shrink (LCST). Hydrogels that are water-loving and thermally sensitive expand at lower temperatures [40].

Chemical stimuli induced pulsatile system

A variety of triggered or PDDS systems may be activated by chemical stress. A biochemical alteration in a human's physiology is employed as a trigger for drug release from the pulsatile system [41].

Glucose responsive insulin release devices

When blood glucose levels rise cyclically as a result of diabetes, insulin must be administered at the proper time to maintain a stable blood glucose level. In response to changes in glucose levels, a variety of systems have been developed. Glucose oxidase is bound in a pH-sensitive hydrogel in one of the systems [42].

Inflammation-induced pulsatile release

Whenever a person receives an injury physical, chemical, stress, fracture, inflammation will occur at the site of the damage. Hydroxyl radicals are created by intemperate-responsive cells during inflammation. Some researchers start working on inflammation sites that induces hydroxyl radicals in a limited manner. The use of hyaluronic acid (HA), which is destroyed by hyaluronidase or free radicals occurs; therefore, hyaluronidase degradation of HA is low in a healthy state. When hyaluronic acid is introduced into an inflammatory location, however, hydroxyl radical degradation is usually quick. Thus there are good possibilities to treat inflammatory disease with anti-inflammatory drug-using HA gel [43, 44].

Drug release from gels responding to antibody concentration

Anatomically, the human body contains a wide variety of physiologically active chemicals. Swelling and de-swelling gels are being developed that respond to changes in bioactive chemical conglomeration. Antigen-antibody complexes were chosen as the gel's cross-linking units because they may serve as the foundation for the construction of a new kind of device [45, 46].

PH sensitive drug delivery system

This process can be used to make tablets, capsules, pellets, and other types of medications. By covering the dosage forms with pH-sensitive polymers, the active medication is protected from gastric fluid and a delayed-release is achieved. Delivery systems are meant to route the medicine to the target place by gathering total polymer information and its solubility at various pH levels. Methacrylic acid and methyl methacrylate are the utmost used polymers for colonic medication administration. Eudragit FS was determined to be better suited for the delivery of ileocolonic medicines during an *in vitro* comparison of Eudragit S and Eudragit FS [47, 48].

Externally regulated system

This pattern of delivering drugs is taken into action by any action of the exterior stimuli. These external stimuli can be means of magnetism, irradiation, electric effect, or ultrasound. Magnetic beads are included in a magnetically regulated system; the supplication of magnetic flux will start drug release because of magnet beads. Unlike formulations that were made earlier in which one is the *in vitro* magnetically generated deliverance of insulin consists of alginate spheres, in the ultrasonically modulated system, ultrasonic waves are showing their action by eroding the polymer matrix, thereby initiating the drug release pattern [49-51].

How circadian rhythm helps in chronotherapy?

So the word Chrono pharmacotherapy comes from Chrono and pharmaceutics; combining these two makes in simpler words makes, chronotherapy. Every metabolic process involves rhythmic variations in time, which is what the name “Chrono” alludes to [52].

The majority of the physiological activities of the human body fluctuate daily, resulting in changes in sick status and plasma medication concentration. Sleep disturbances and increased discomfort are caused by the body's peak hormone levels. The human sleep activity cycle, also known as solar/lunar adaptations, is governed by the circadian rhythm, which is influenced by an individual's genetic composition and is responsible for determining physiological processes. Every metabolic process involves rhythmic variations in time, which is what the name "Chrono" alludes to. Furthermore, a new study has suggested that circadian regulation affects gene expression in a major way [53]. A significant number of genes expressed in cells or tissues (about 10%) have been discovered to contain circadian oscillations, leading to the designation of these genes as clock-controlled genes (CCGs) [54]. It is obvious that, rather than simply maintaining constant medication concentrations, drug delivery and treatment should be adjusted to reach effective drug intensity at the optimal time. As a result, third-generation DDSs' time-controlled capacity is being used to develop novel and upgraded disease cures [55]. Internal biological clocks linked to the sleep-wake cycle are used to synchronize circadian rhythms. Shortly, there is a lot of optimism for effective pharmacological therapy using chronopharmacology. So the last term which comes into consideration is that circadian rhythm is the most crucial parameter to determine asthma disease and others too for achieving chronotherapy as shown in (fig. 5) [56, 57].

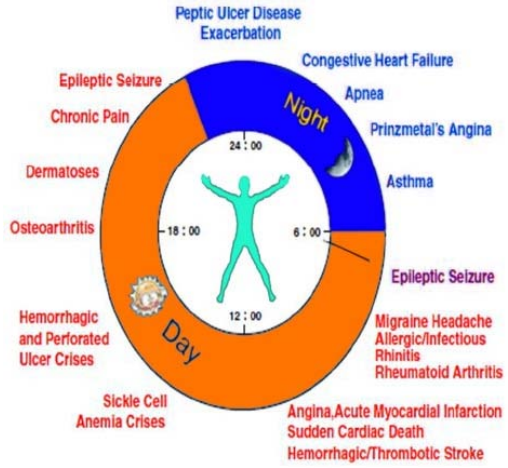

Fig. 5: Biological rhythm indicating various diseases [45]

Pharmaceutics

Pharmacology is the field of pharmacy that deals with transforming a chemical entity into a drug that may be used safely and successfully by the patient in the treatment of any illness or condition. In the pharmaceutical industry, this is also known as the science of dosage form and commerce.

Chronotherapy

The investigation of the biological clock and its executions is characterized as chronotherapy. Mechanical rhythms in the human body often fall into one of three categories.:-

a) Circadian: the word 'circa' indicates about and 'dian' indicates day.

b) Ultradian: the swing of smaller onset is named ultradian (more than 1 cycle per 24 h).

c) Infradian: oscillations that are termed to be more than 24h (under one cycle per day).

For the conduct of certain activities, all endogenous organic processes and some other tasks are programmed for a time length of 24 h. Living creatures are made up of a variety of rhythms with different frequencies ranging from seconds to seasons [58, 59].

Asthma

The importance of biological rhythms in the treatment and etiology of asthma suggests that in asthmatic patients, resistance in the airways of the lungs increases gradually at night [60]. In normal lung function, circadian or biological variations are observed; afterward, the lowest point of asthma occurs in the morning period, i.e., from 4 a. m. onwards. This kind of pronunciation is usually for people suffering from asthma because exacerbation and Bronchoconstriction are the symptoms that vary in circadian rhythms, which clearly shows that asthma is well suited for chronotherapy [61]. Medication that is taken at specific times can improve its efficacy while lowering its toxicity. Inhaled and oral corticosteroids, extended-release medication such as theophylline, prolonged-acting b-agonists, leukotriene-modifying medicines, and anticholinergic medications are among the treatments available [62]. New methods for disease management and improved patient care have resulted from a better consideration of the Chrono biological effect on asthma pathology, as well as the pharmacology and pharmacokinetics of the medications used to treat it as shown in (fig. 6) [63]. Because bronchoconstriction and symptom aggravation change on a diurnal basis, PDDS has been proven to be a good target for chronotherapy [64].

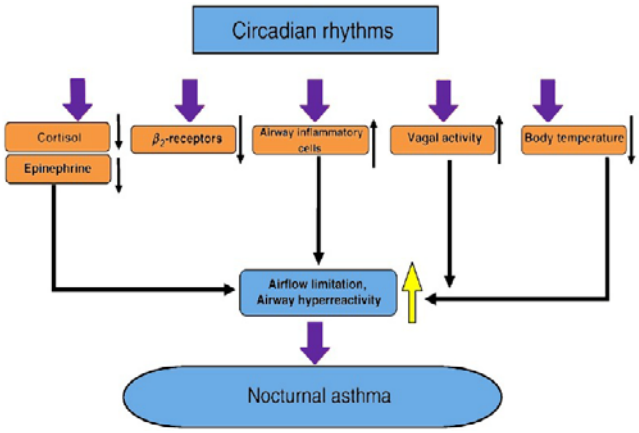

Fig. 6: Mechanism underlying worsening of asthma [68]

Potential mechanisms leading to nocturnal asthma

(a) Increased airway parasympathetic tone.

(b) Decreased lung capacity.

(c) Unloading of airway smooth muscle.

(d) Actin–myosin binding is disrupted.

(e) Respiratory function modulation by the 24-hour clock.

(f) A lower rate of expiratory flow.

(g) Catecholaminergic activity is decreased.

(h) A reduction in cortisol.

(i) A rise in pro-inflammatory cytokines.

(j) Environmental elements that affect sleep.

(k) Allergen.

(l) Air that is frigid.

(m) A comorbid disease is a sickness that affects more than one person.

(n) Obstructive sleep apnea (OSA).

(o) Impede.

(p) GERD (gastroesophageal reflux disease) [65].

Antigen challenge responses of prior, late, and recent nocturnal asthma

There are three stages to an asthma attack: the first attack, the secondary attack, and the recurring nocturnal attack. the EAR is defined by a slight and brief reduction in airway tone as demonstrated by FEV1 changes from the base point and begins within minutes of the antigen exposure, the major early-phase asthma response (forced expiratory volume in 1 s). For example, histamine and particular leukotrienes are released from hepatic mast cells to activate the EAR, which is similar to the early phase response reported in challenge trials on AR patients' upper airways. As a consequence of the increased use of bronchodilators and anti-inflammatory medicines at similar doses in the airways, it is more harmful than EAR and necessitates a much larger fall in airline tone (reduction in FEV1) than EAR [66].

Research on asthma revealed by linking circadian rhythm and sleep

When it comes to the circadian and sleep systems in asthma, there has been a long-running debate over their respective properties. Furthermore, the nightly reduction in airway function does not imply that a brain regulatory mechanism associated with sleep is abnormal. For starters, asthma seems to be affected by both circadian and sleep aspects. Airway function is at its peak in the afternoon when people are most sleepy, and it declines when sleep deprivation sets in at night. Even though asthma seems to be linked to a lack of sleep, many asthmatic individuals also have sleep difficulties. There is evidence that patients suffering from asthma or chronic lung illness have difficulty falling asleep, have poor sleep quality, and are excessively tired throughout the day. The findings of significant recent research show that asthmatics are more likely to report difficulty initiating sleep, early morning awakenings, daytime drowsiness, and daytime exhaustion, even after adjusting for some of the aforementioned characteristics. Even though asthmatics have a much worse sleep efficiency than healthy persons, studies show that asthma has minimal effect on sleep latency or sleep stage distribution. As a consequence, asthmatic persons find it difficult to sleep [67–69].

Asthma severity assessment or evaluations

Peak expiratory flow (PEF) is used to measure the severity of an asthmatic's illness since it has a greater daily fluctuation than that of a healthy person. PEF is tested at least twice a day, around midday and an hour before bedtime, and changeability is calculated as the ratio of the highest and smallest PEF differences divided by the average of all measurements taken that day. When PEF rises or falls, or both, it suggests that asthma is becoming better or worse [70].

Chronotherapy for asthma

The majority of asthma medications are taken only once at night, to prevent chronic airway inflammation or the development of airflow restriction. These medications make it simple to treat nocturnal asthma at home and a once-daily dose at night increases patient compliance [71]. Patients' particular needs can be met by giving drugs at the right time of day. Chronotherapy or pulsatile drug delivery is a more reasonable manner of treatment that maximizes efficacy while reducing negative side effects. To carry out asthma chronotherapy with optimal efficacy, it is necessary to analyze the blood concentration profile of a drug above time and make sure that the drug concentration is sufficient when intensified symptoms are predicted [72].

To far, theophylline extended-release tablets and 2-agonists have shown to be the most effective bronchodilators for chronotherapy. Snuff corticosteroids were shown to be virtually as effective as four daily dosages in another research. Chronic airway inflammation reduction is another important chronotherapy target. Inhaled corticosteroids, according to the GINA analysis, might be a more effective way to treat asthma [73]. When it comes to asthma, pulsatile drug delivery systems are used to release the medicine at a precise moment and in the correct quantity, as indicated in table No. 2, which illustrates some asthma medications.

Table 2: Illustration of some FDA-approved chronological drugs for the treatment of asthma in the market

API	Category	Proprietary name and dosage form	Manufacturer
Theophylline	Xanthine derivative, Bronchodilator	Uniphyl®/Uniphyllin® Sr Tablets	Purdue frederick, USA; Mundipharma, Germany
Salmeterol	B2 Adrenergic Agonist	Sustained Effect Aerosol	Glaxo Uk And USA
Formoterol	B2 Adrenergic Agonist	Sustained Effect Aerosol	Ciba Geigy, Europe
Bambuterol	B2 Adrenergic Agonist	Multilayered SR Tablet Bambec®	Astra Draco, Sweden
Ciclesonide	Glucocorticoids	Alvesco®, Metered Dose Inhale	Teijin Pharma Ltd. Japan
Tulobuterol	B2 Adrenergic Agonist	Hokunalin® Tape, Transdermal Patch	Abbott, Japan
Methyl Prednisolone	Corticosteroid	Medrol®	Upjohn, USA
Cromolyn Sodium	Mast Cell Stabilizer	Intal®	Fiscons, Uk
Nedocromil Sodium	Mast Cell Stabilizer	Tilade®	Fiscons, Uk
Terbutaline	B2 Adrenergic Agonist	Bricanyl Depot®, Sr Tablet	Ab Draco, Sweden
Theophylline	Xanthine derivative, Bronchodilator	Euphylong®, Sustained release Tablets	Byk, Gulden, Germany

Some formulations described in previous articles used in the treatment of asthma are prepared by the action of a pulsatile drug delivery system

Salbutamol

Salbutamol works by relaxing bronchial smooth muscle by activating the β2 adrenergic receptors [74].

J Qureshi, Mohdamir *et al.* 2008 discovered that the swelling layer includes HPMC E5 of different w/w concentrations in which 20% w/w is considered to be optimum for the formulation of asthmatic drug followed by another parameter which is eudrgait outer layer coating. The coating done on the tablet was of range 4 and 6 mg/cm^2 which shows a complete and fast release. The higher coating level 8 and 10 mg/cm^2 shows slower release after lag time due to decreased degree of tearing. There was no discernible dissimilarity in drug release when the release study was conducted at different pH levels or varying rotational speeds. This is a benefit for the system because it anticipates no changes in system performance as stomach motility increases. The coated tablet exhibited a smooth and tight surface,

according to scanning electron microscopy. According to accelerated stability experiments, the product has a shelf life of 1.9 y [75].

Theophylline

Two factors and three levels of full factorial design were utilized for the optimization of theophylline pellets in 2010 by Vinayak D. Kadam *et al.* Research was done on the dissolving rate of several compounds in the simulated digestive tract, intestines, and colonic fluid. Lag time before drug release might be significantly reduced by using Eudragit RL100 aggregate in polymer blends and increasing coating levels. With a coating level of 12 percent w/w, a mixture of Eudragit S 100 and Eudragit RL 100 was determined to be the most effective. According to this research, a pH-and time-dependent modified Chrono pharmacological formulation may effectively target the colon for the treatment of asthma using theophylline enteric-coated pellets [76].

Doxofylline

Dali Shukla *et al.* in 2012 signifies research that the *in vivo* pharmacokinetic investigation of a prolonged-release pastille formulation revealed a notable drop in Cmax with an expansion in tmax, showing that the dosage form's impact will continue longer. As a result, the produced formulation could be beneficial in the long-term treatment of asthma and COPD. The g-scintigraphy investigation and pharmacokinetic results showed clear evidence that the pastilles coated with the enteric coat and the extra floating coat were successful in delaying the *in vivo* medication release required for the Chrono treatment of nocturnal asthma (by 4--5 h) [77].

Tiotropium bromide

C. Murali Krishna Goud and Y. Sravani *et al.* represented a research work in the year 2012 for several physicochemical criteria such as hardness, friability, thickness, and weight fluctuation, all of the formulations produced good results in the studies of the research work. The lag time is mostly affected by ethylcellulose, but it also has a substantial impact on drug release. A delayed release design is visible on a press-coated tablet. Superior (T7) was chosen from among all of the basic tablet formulations based on drug release over a set length of time. (P3T7) formulation which is considered as best of other formulations was optimized based on less drug release during lag time, according to *in vitro* release rate tests. For 6 mo, Formulations (P3T7) were shown to be stable at 45degree Celsius and 75% RH. Tiotropium bromide had no interaction with the polymers, according to FT-IR measurements, and is shown to have good chronotherapy for asthma tolerant [78].

Zafirlukast

For the first time, researchers in 2021 have discovered a new method for making tablets by compressing them directly with numerous super-disintegrants and then coating them in natural polymers. They fulfilled the Pharmacopoeia's limit for pre-and post-compression properties for tablets. Xanthan gum and dammar gum as a barrier layer for delaying the release of the medicine from the tablet was shown to yield results equivalent to the needs of asthma patients' chronotherapy *in vitro* release trials [79].

Montelukast sodium

A 4-hour delay in optimal pulsatile release capsule formulation resulted in 61.95 percent and 96.29% of their contents being released at 6 and 12 h, respectively. When animals like rabbits were fasting, X-ray radiography imaging was employed to follow the *in vivo* behavior of barium sulfate-loaded pulsatile release capsules. Tmax for marketed tablets was found to be 2 h in an *in vivo* pharmacokinetic investigation, whereas Tmax for PRCs was shown to be 7 h (pulsatile release capsules). These patients may benefit from the capsular system, according to research done by Om Prakash Rajan *et al.* in 2013 [80].

Future aspects

The future of drug delivery in a pulsatile way will soon be a boom for the pharmaceutical industry and will have a great and good impact in the chronotherapy field. It has the majority of advantages when compared with the traditional system. The right criteria are the delivery of the drug at right time and the right dosage is the one that puts pulsatile drug delivery aside from others. The usage of polymer and other active ingredients in an adequate way for the pulsatile formulation will be the most advantageous and can be modified more for future aspects and discoveries. More rapid and newer developments can be established for the treatment of asthma in the coming time by using pulsatile techniques. Tomorrow's medication going to be more challenging in terms of drug delivery so the pharmaceutical must be ready for this upcoming task.

CONCLUSION

This article focuses on asthma concepts and chronotherapy to increase drug safety and effectiveness. Traditional drug delivery systems are less beneficial when it comes to pulsatile drug delivery because the system works based on circadian rhythms that indicate the time and location in which a drug should be administered. Pulsatile drug delivery is also more potent because it begins to take effect more quickly. Asthma sufferers benefit the most from this administration since it is simple and painless, and it has great potential for treating asthma and other disorders as well. You may expect the finest potential results and outcomes for asthma sufferers using the methods outlined in this article. Inhaled corticosteroids and theophylline are two common stays of asthma chronotherapy. New medications aren't the sole option for treating asthma, but the enhanced application of current treatments in a new method, as well as the modification of polymers and other substances, may make the medicament more effective and beneficial in the treatment of asthma.

ACKNOWLEDGEMENT

The authors are thankful to the Noida Institute of Engineering and Technology (Pharmacy Institute), Greater Noida–201 306, Uttar Pradesh, India, for providing all necessary support and facilities to conduct the survey related to the present review.

FUNDING

Nil

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICTS OF INTERESTS

The authors have reported no conflicts of interest.

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