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Review Article

CHRONOTHERAPY OF NOCTURNAL ASTHMA AND RECENT PATENTS: A REVIEW

Prabhjot Singh Bajwa[1*], Jaya Sharma [2], Anurag Bhargava [1], Shailesh Sharma [3], Abhimanyu Rai Sharma [1]& Binu Sharma[1]

[1] Ch. Devilal College of Pharmacy, Jagadhri, Yamunanagar, Haryana, India.

[2]School of Pharmaceutical Sciences, Jaipur National University, Jaipur, Rajasthan, India

[3] Department of pharmaceutics, Amar Shaheed Baba Ajit Singh Jujhar Singh Memorial College of Pharmacy, Bela, Ropar, Punjab, India.

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ABSTRACT

The study of biological rhythms is called chronobiology. Many diseases have been found to show rhythm in their symptoms and severity. To treat such diseases the timing of drug administration is matched with circadian rhythms of the disease and such treatment is called chronotherapy.

Asthma is one of the many diseases showing rhythmicity in its symptoms. Night time worsening of asthma has been reported in literature from early times. For the effective management of asthma patient needs to take medicine so that effective concentration of the drug is maintained throughout the night especially during early morning hours.Chronotherapy of asthma has been done using various drugs which include β2-adrenergic agonist medication such as short acting β2-adrenergic agonist (SABA) and long acting β2-adrenergic agonist (LABA). Terbutaline sustained release tablet formulation was one of the first to be assessed in chronotherapy trials. Other drugs to be studied for chronotherapy are theophylline, prednisolone (Systemic corticosteroids), Tiotropium (anticholinergic agent), Montelukast, Pranlukast, and Zafirlukast (leukotriene receptor antagonists). Chronotherapy of nocturnal asthma has shown promising results but right dosing and timing is necessary to yield such results. Chronotherapeutic drug delivery systems are formulated to achieve the right time delivery of the drugs to match biological rhythms of the disease. Different formulation strategies are followed to achieve such delivery.

Present review outlines the basics of chronotherapy along with chronotherapy of Nocturnal asthma and patents granted for chronotherapeutic drug delivery systems for asthma.

Keywords: Nocturnal asthma; chronotherapy; circadian; chronotherapeutic.

Introduction

As the science of medicine developed the concept of homeostasis was solely used to treat diseases. This theory states that the symptoms occurrence and exacerbation of disease do not depend on the time of day, the day of the month, and month of the year as the response of patients to diagnostic tests and medications. However, new findings from the field of biologic rhythm study challenge the concept of homeostasis. It is now recognized that most of the human functions are precisely organized in time as biological rhythms and are repeated after a period of 24 h, weeks, months, or even years.[1,2]

Chronobiology

Chronobiology is defined as the study of biological rhythms and their mechanisms. From ancient times relation between time and biological functions has been studied. As early as the fourth century BC, Alexander the Great's scribe Androsthenes noted that the leaves of certain trees opened during the day and closed at night showing a clear rhythmicity. In 1729, the French astronomer Jean Jacques d'Ortous deMairan conducted the first known experiment on biological rhythms. The term ''circadian'' was coined by Franz Halberg from the Latin circa, meaning about and dies, meaning day. Circadian means showing rhythmic behaviour.[3-5] Many biological functions such as nerve impulse,

*Corresponding author: Prabhjot Singh Bajwa | E-mail: prabhjot.bajwa1@gmail.com

heartbeat, sleep, menstrual cycles show rhythmic behavior. The time between each repetition of such biological functions is called as aperiod.

A biological rhythm is a self-sustaining oscillation with the period, that is theamount of time between each repetition. The biological rhythms can be grouped into three categories.

1. High frequency (0.5 s-0.5 h): Examples electrocardiogram, nerve impulses.

2. Medial frequency: Examples rest activity, sleep-wakefulness.

a) Ultradian (2 h-20 h).
b) Circadian (20 h-28 h).
c) Infradian (28 h-6 days).

3. Low frequency (> 6 days): Example menstruation.

a) Circaseptan (~7 days).
b) Circamensual (~1 month).
c) Circannual (~1 year).

Usually, the circadian rhythms have a period of 20 to 28 h between each repetition. Many thousands of articles have been published in highly respected scientific, medical, and pharmacology journals over the past several decades documenting biological rhythms in humans and animals. [6-9]

Mechanisms of biological time-keeping

Biological rhythms are controlled by an inherited master clock network composed of the paired suprachiasmatic nuclei (SCN) situated in the hypothalamus and pineal gland.[10-13]Clock genes, Per1, Per2, Per3, Bmal, Clock, and Cry, and their gene products comprise the central timekeeping mechanism and are responsible for rhythmic activities in the SCN.

Transcription factors CLOCK and BMAL1 drive the expression of Per1, Per2, Cry1, Cry2, plus a variety of clock-controlled genes via E-box sequences in their promoters. Negative feedback of PER and CRY proteins on thetranscriptional activity of CLOCK:BMAL1, results in a circadian rhythm in theexpression of the CLOCK:BMAL1 driven clock and clock-controlled genes.Accessory feedback loops involving the genes Rev-erba and Rora. are responsible for the stabilization of rhythm. The precision of the period of circadian rhythms is achieved via posttranslational modulation of the clock proteins by cyclic environmental time cues, the most important being the 24 h environmental light–dark cycle.[14]The biological time-keeping system also includes the multitude of peripheral circadian clocks located in cells, tissues, and organs, which are regulated by the master SCN clock.[11] The output of the central and peripheral circadian clocks is mediated by various clock-controlled genes, giving rise to the body's circadian time structure (CTS).

Chronopharmacology: biological rhythms and medications

The timing of medication has a considerable effect on its pharmacokinetics and pharmacodynamics, no matter their route of delivery. Chrono-pharmacology is defined as the study of the manner and extent to which the pharmacokinetics and pharmacodynamics of medications are affected by endogenous biological rhythms, and also how the time of dosing affects biological time keeping and circadian time structure.[12-17]

Chronotherapeutics

Chronotherapeutics is defined as the purposeful delivery of medications in time to meet biological-time determinants of disease pathophysiology (chronopathology) and chronopharmacology (chronokinetics, chronodynamics, and chronotoxicology) of medications to optimize outcomes and minimize/avoid adverse effects.[12-13] Chronotherapeutics may involve improved delivery of established therapies or new medicines. Chronotherapeutics can be achieved by unequal morning and evening dosing schedules of conventional sustained release 12 h tablet and capsule systems, optimal timing of conventional once-a-day delivery systems, or application of special drug-delivery systems to proportion medications over the 24 h cycle in order to meet rhythm determined requirements. To achieve desired outcome patients should adhere strictly to dosing time with reference to the sleep–wake cycle. Also, theclinical community should have a sound understanding of the concepts of chronobiology and chronotherapeutics for the success of the chronotherapies.[18]Chronotherapy can be done for many diseases such as nocturnal asthma, rheumatoid arthritis, hypertension, pain, cancer etc. This study is focussed only on Nocturnal asthma.

Asthma

The National Asthma Education and Prevention Program (NAEPP) define asthma as a chronic

inflammatory disorder of the airways in which many cells and cellular elements play a role. In susceptible individuals, inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and coughing. These episodes are usually associated with airflow obstruction that is often reversible either spontaneously or with treatment.[19]

Asthma is a common disorder, accounting in the United States for 1% to 3% of all hospital visits, 500,000 hospital admissions per year moreover asthma accounts for most paediatric hospital admissions than any other single illness and more than 5000 deaths annually.[20]

Characteristics of asthma

Asthmatic patients experience intermittent attacks of wheezing, shortness of breath with difficulty especially in breathing out and sometimes cough. As explained above, acute attacks are reversible, but the underlying pathological disorder can progress in older patients to a chronic state superficially resembling COPD. Acute severe asthma (also known as status asthmaticus) is not easily reversed and causes hypoxaemia. Hospitalisation is necessaryin such conditions which can be fatal and requires prompt and energetic treatment.

Asthma is characterised by:

- Inflammation of the airways.
- Bronchial hyper-reactivity.
- Reversible airways obstruction.

The term bronchial hyper-reactivity (or hyper-responsiveness) refers to abnormal sensitivity to a wide range of stimuli, such as irritant chemicals, cold air, and stimulant drugs, all of which can result in bronchoconstriction.[21]

The main symptom of asthma is difficult breathing due to reduced airway caliber, bronchospasm and excessive secretion of mucus. Asthma is a reversible airways disease since the abnormally low airflow rates can be partial or fully restored by prescription bronchodilator and anti-inflammatory medications.

Chronobiological aspects in asthma

Asthma is one of the many diseases showing circadian variation. Night time worsening of asthma has been reported in theliterature from ancient times. Soranus of Ephesus in 2nd century AD reported the night time worsening of asthma but it was it was Caelius Aurelianus in the 5th century who first reported on the daily variation in asthma attacks in a chapter entitled “De Suspirio, siveAnhelitu, quemGraeci Asthma vocant” — “Gravat autematquepremithaecpassiomagismulieribusviros, & juvenibussenes, atquepueros, & durioribus natura corporisteneriora, hyberno, atquenoctemagis, quam die vel aestate.” (“On the heavy breathing and wheezing which is called Asthma by the Greeks”: “This disease is a burden, and men suffer more than women, and elderly more than the young … during winter and in spring person suffers more at night than during the day time”.) At the end of the 18th century, John Floyer a medical doctor who had suffered for 30 years from Asthma wrote: “I have observed the fit (asthma) always to happen after sleep in the night”. The severity of BA varies between patients and even in the same individual over time. Most persons experience the worsening of their asthma during the night, and many experience asthma only at night.[22]

It has been demonstrated by Dr. Turner Warwick in a study on alarge population of almost 8000 asthmatic patients that 39% had symptoms of asthma every night, 64% at least three nights per week and 74% at least one night per week.

From the literature, it has been found that lung function in anormal subject is at it’s best around 4pm and worst around 4am with about 8% change in the normal population.

The peak flow rates of the asthmatic patients are about at 4 pm and lowest at about 4am. The asthmatic population, however, can have much more dramatic overnight decrements in lung function than the normal population.[23]Impairment due to asthma can have a substantial impact on quality of life.[24]

Factors used in evaluating severity of asthma

Mainly two factors are used in evaluating the severity of asthma

1. PEF (peak expiratory flow rate)
2. FEV_1 (forced expiratory volume in 1 s)

1. **Peak expiratory flow rate** (PEF) is the greatest airflow velocity that can be produced during a forced expiration that starts from fully inflated lungs.[25-26]Daily variability in PEF is larger in asthmatics than in healthy subjects and is used as

an index of the activity of the disease process. PEF is measured daily at least in morning, in noon and at night before going to sleep; variability is expressed as the ratio of the difference between the highest and lowest PEF divided by the average of all measurements that day. An improved or lower level of PEF of its variability, or both signifies improvement or deterioration of asthma.

2. **Forced expiratory volume** (FEV_1) is the amount of air which can be forcibly exhaled from the lungs in the first second of a forced exhalation.[27]It has been recommended by the expert panel that the spirometry measurements of FEV_1, FEV_6(Forced expiratory volume in 6 seconds), FVC(Forced vital capacity) and FEV_1/FVC should be performed and before and after the patient inhales a short-acting bronchodilator should be undertaken for patients in whom the diagnosis of asthma is being considered, including children ≥5 years of age. FVC is the total amount of air exhaled during the FEV test. These measurements help to determine whether there is airflow obstruction, its severity and whether it is reversible over the short term. Abnormalities of lung function are categorized as restrictive and obstructive defects. A reduced ratio of FEV_1/FVC or FEV_1/FEV6 indicates anobstruction to the flow of air from the lungs, whereas a proportionately reduced FVC (or FEV6 in adults) with a normal or increased FEV_1/FVC (or FEV_1/FEV_6) ratio suggests a restrictive pattern. The severity of abnormality of spirometric measurements is evaluated by comparison of the patient's results with reference values based on age, height, sex and race.[28]

Mechanisms of nocturnal asthma

The mechanism behind nocturnal asthma is complex but day time exposure to stimuli such as pollens, dust, smoke etc. causes release of pro-inflammatory mediators from mast and eosinophil cells over the span of several hours thereafter, which results by the end of the day in the exacerbation of inflammation, smooth muscle bronchospasm and contraction, and over-stimulation of mucus glands which causes hypersecretion of mucus in the small airways of the lung. All these processes can be modulated by neuroendocrine and other important high amplitude circadian rhythms, such as those of the hypothalamic–pituitary–adrenocortical (HPA) and autonomic nervous systems.[22]

Circadian Variations in Lung Function-

It has been found in a study that both asthmatic and healthy subjects reliably demonstrate their lowest PEFR in the early morning hours; however, the asthmatic subjects have much lower PEFR values indicating more severe bronchospasm. The peak-to-trough swings in peak expiratory flow rate in this study were only 5% to 8% in healthy controls compared to 50% or more in asthmatic individuals.

- **Beta-receptor regulation-**One study compared asthmatic individuals with and without nocturnal symptoms to healthy controls and showed that at 4 am compared with 4 pm, only patients with nocturnal asthma had a significant decrease in beta-adrenergic receptor density; however, there was no difference in binding affinity in all three groups. This downregulation in nocturnal asthmatic individuals may have a genetic basis.

- **Inflammatory changes at night-**In a study it has been found that nocturnal asthmatic individuals have an increase in the total leukocyte count, neutrophils, and eosinophils from 4 pm to 4 am; however, cellular components from a non-nocturnal asthma control group did not change. This study suggests that the nocturnal worsening of asthma has an associated cellular inflammatory response that is not seen in patients without overnight decrements in lung function.

- **Variation in the parasympathetic nervous system-**Increased vagal tone during sleep could promote increased bronchoconstriction. There is a diurnal variation in avagal activity that has been demonstrated in asthmatic patients, with higher vagal activity occurring at night.

- **Neurohormonal changes-**It has been found that there is a significant circadian variation in the levels of various neurotransmitters and hormones. Histamine, which is a potent bronchoconstrictor, has been shown to be significantly lower in healthy individuals during sleep when compared with asthmatic individuals. Melatonin, which is an endogenous sleep-inducing hormone, has been shown to be higher in asthmatic individuals with nocturnal symptoms as compared to healthy individuals. Melatonin also has been shown to be correlated inversely with lung function in nocturnal asthmatic individuals and to have pro-inflammatory properties.[29]

Chronotherapy in asthma

Chronotherapy of nocturnal asthma may be accomplished by synchronizing drug concentrations to rhythms in disease activity, this leads to increased efficacy as well as reduces adverse effects. The effectiveness of chronotherapy for asthma can be seen by its effect on the morning dip in the lung function measurements of PEFR or FEV_1.When there is poor management of asthma, the morning PEFR is markedly lower than the evening PEFR. Most of the drugs that are currently used chronotherapeutically are administered once at night with the goal of preventing chronic airway inflammation or the onset of airflow limitation. The benefit of once-daily dosing is that it improves patient adherence and also promotes self-management of asthma.[30]

Current and emerging chronotherapies for asthma

β-2 Adrenergic Receptor Agonist medication:

β-2 agonists primarily cause relaxation of airway smooth muscle, to increase airway caliber and relieve bronchoconstriction. However, β-2 agonists also have an anti-inflammatory action.[31-32]

Mostly BAs are inhaled and are of two types: -

1. Short-acting β-2 agonists (SABA) with a duration of around 4 hours.
2. Long-actingβ-2 agonists (LABA) effective for 12-24 hours.

SABAs are prescribed as "reliever" medications for immediate relief from bronchoconstriction. The majority of LABAs are inhaled as aerosols (the advantage being delivery directly to the target area with fewer systemic side effects). LABAs can also be administered orally as tablets and as a transdermal preparation in the form of patches.

LABA tablet formulation

Terbutaline (Bricanyl Depot®, AB Draco, Sweden) is a LABA tablet formulation that was one of the first to be assessed in chronotherapy trials. Five milligrams were administered in the morning (8 am) when the lung function was beginning to improve to its best level in the afternoon. Ten milligrams were administered in the evening (8 pm) when lung function was beginning its decline to its worst level in the early hours of the morning. This chronotherapeutic strategy significantly increased the 24-hour mean PEFR and FEV_1 and almost completely averted their characteristic nocturnal decline.

Bambuterol (Bambec®, Astra Draco, Sweden) is a prodrug of terbutaline and exerts a bronchodilator effect for 24 hours. A chronotherapeutic trial of bambuterol investigated once-daily dosing with 20 mg in the morning, versus the evening, versus placebo. Evening dosing resulted in a considerably higher morning FEV_1 and PEFR. Overall, evening dosing was more advantageous because it improved FEV_1 throughout the 24 hours to a greater extent than morning dosing.[33-35]

LABA inhaler medication

Formoterol (Novartis, Basel, Switzerland) and salmeterol (GlaxoSmithKline plc, London, UK, and the USA) are aerosol LABA medications, with few adverse effects. Both medications have aduration of action of about 12 hours, although formoterol may have a more rapid onset of affect.[36-37]

Formoterol and salmeterol are similar in chemical structure, except that salmeterol possesses an elongated side chain that binds the molecule firmly to the β-2-adrenoceptor, allowing it to repeatedly excite the receptor.[38]Overall, the results of many large-scale studies demonstrate that twice daily, 12-hour interval dosing of 50 µg salmeterol, compared to the dosing of 180–200 µg Albuterol four times daily, results in better control of overnight and morning PEFR and FEV_1, reduces daytime and night time asthma frequency.[30]

Anticholinergic agents

The cholinergic tone from vagal nerves in the parasympathetic system increases at night and may cause bronchoconstriction and mucus secretion.[22,25]

Short-acting muscarinic antagonists (SAMAs) include ipratropium bromide and long-acting muscarinic antagonists (LAMAs) include tiotropium, aclidinium, and glycopyrronium. Of the LAMAs, tiotropium is the most widely studied in asthma. Tiotropium is an anticholinergic medication that dissociates slowly from the muscarinic M3 receptor, found on bronchial smooth muscle. It, therefore, has a prolonged duration of action of more than 24 hours. It can be inhaled as a dry powder (Handihaler®, Boehringer Ingelheim, Ingleheim am Rhine, Germany) or as a fine particle mist (Respimat®, Boehringer

Ingelheim, Ingleheim am Rhine, Germany). Tiotropium has been shown to be an effective asthma treatment in patients.[39]

Synthetic corticosteroid medication

Inhaled corticosteroids are recommended as a first-line treatment. Corticosteroids exert direct inhibitory effects on macrophages, T-lymphocytes, eosinophils, plus airway epithelial and other cells involved in airway inflammation. Corticosteroids decrease eosinophil cell numbers, especially those associated with the inflammation process, by inducing apoptosis, and they reduce airway mast cell density. Also, they inhibit mucus secretion, plasma exudation, and airway tissue re-modelling. The chronotherapy of aerosol and tablet cortico-therapies have focused on three major concerns: -

1. Control of adrenocortical (cortisol) suppression.
2. Improvement of airway caliber (PEF and FEV1) especially during the night and in the early morning.
3. Control of nocturnal bronchial asthma.[30]

Oral corticosteroids

Beam et al, conducted a double-blinded, placebocontrolled, crossover protocol to study the effect of either 50 mg prednisolone or placebo given at 8 am, 3 pm or 8 pm on FEV1 in patients with uncontrolled nocturnal asthma and found that 50 mg prednisolone dose attenuated the nocturnal decline in FEV1 only when ingested at 3 pm. The ingestion of 50 mg prednisolone at 8 am or 8 pm was ineffective.[40]

Inhaled corticosteroids (ICSs)

The advantage of inhaled therapy is that corticosteroid is delivered specifically to the target area. However, this is dependent on the ability of the subject to correctly use the inhaler device; deposition of the ICSs in the oropharynx will lead to increased systemic absorption and the development of associated side effects.

Several studies have investigated the chronotherapy of ICSs. In one study, triamcinolone acetate aerosol when given to asthmatics at 3 pm (800 µg) was found to be at least equivalent compared to the conventional four-times-a-day (200 µg) treatment schedule.[41]

In a second study, Pincus *et al*. compared four-times-a-day triamcinolone acetate (800 µg/day) with single 8 am or 5.30 pm once-daily dosing regimens in moderately severe nocturnal asthmatics. Both the four-times-a-day and the 5.30 pm dosing regimens improved the morning and evening PEF in a comparable manner, but not the single 8 am dose.[42]

Once-daily ciclesonide (160 µg dose) has been shown to be as effective as twice-daily (88 µg dose) fluticasone in improving airway caliber, controlling asthma symptoms and reducing reliance on rescue medication.[43]

Theophyllines

Theophyllines, have a weak bronchodilator effect and a significant anti-inflammatory effect. It has been found that in asthmatic patients, theophylline inhibits the late response to an allergen, increases CD8+ cells in peripheral blood, and decreases T lymphocytes in the airways (44,45).

In the 1980s Euphyllin® (Byk Gulden, Konstanz, Germany) was developed as a sustained release, asymmetric morning–evening dosed theophylline preparation (46). But, the asymmetric dosing schedule reduces patient adherence, and therefore once-daily preparations were developed. Euphylong® (Byk Gulden) and Uniphyl® (Purdue Frederick, Stamford, CT, USA)/Uniphyllin® (Mundipharma, Limburg, Germany) are dosed at night with the intention of achieving peak concentration overnight/early morning when the drop-in PEF is the greatest.[47]

Leukotriene receptor antagonists

The leukotriene receptor antagonists (Montelukast, Pranlukast, and Zafirlukast) and the 5-lipoxygenase inhibitor zileuton are a new class of anti-inflammatory drugs that reduce leukocyte traffic and modulate airway inflammation and bronchial hyper responsiveness.[48,49]

Montelukast is recommended for ingestion once daily in the evening; however, it is not marketed as a chronotherapy. A double-blind study showed that Montelukast better improved FEV1 when dosed in the evening rather than morning[50], and a second study confirmed this and also showed that even once-daily, low-dose (10 mg) of Montelukast in evening improves asthma. Zileuton was initially formulated to be taken four times a day; however, an extended-release tablet is now available with

twice-daily dosing. Zileuton therapy is monitored because of the risk of hepatic toxicity.[30]

Chronotherapeutic drug delivery systems.

Chronotherapeutic drug delivery systems are formulated to deliver drug to match timings of the disease. The delivery of drugs can be done either after a lag-phase or can be sustained release. The delivery after lag phase is done for diseases whose symptoms are pronounced at midnight or in early morning and sustained release delivery is done when the effective concentration of drug is to be maintained thought the night. Different formulation strategies can be adopted to get release in this manner. Generally speaking, for release after a well-defined lag-time, a core is formulated with some superdisintegrants or an effervescent salt which is coated with releases delaying polymer and for a sustained release the drug is either entrapped in a slowly eroding/releasing polymer or an osmotic capsule that slowly releases the drug.[51-53]

Patents granted for chronotherapeutic drug delivery systems.

A large number of patent have been granted for chronotherapeutic drug delivery systems but only the patents linked to chronotherapy of asthma are discussed here.

Baichwal et al.formulated a chronotherapeutic pharmaceutical formulation comprising a core containing an active agent and a surfactant and a delayed release compression coating comprising a natural or synthetic gum applied onto the surface of the core. That is capable of delaying the release of drug from dosage form until after a period of time from about 2 to about 18 hafter exposure of the dosage form to an aqueous solution. The polymers used in compression coating are xanthan gum and locust bean gum. Surfactants that may be used in the present invention generally include pharmaceutically acceptable surfactants for example, monovalent alkyl carboxylates, acyl lactylates, alkyl ether carboxylates, N-acyl sarcosinates. Author's mentioned that the aforesaid formulation can be used in chronotherapy of asthma, arthritis, hypertension and other disease whose symptoms are more acute in morning.[54]

Dipierro *et al.* invented an automated, pre-programmable transdermal administration system which can be used to provide pulsed doses of medications, pharmaceuticals, hormones or another physiological active ingredient or precursor. The system is micro-processor controlled and can pump active ingredient transdermally at the required time. The permeation of active ingredient through the skin can be assisted by pre-treatment with and/or using micro fabricated structures commonly referred to as micro-channels, micro-needles, heating devices, iontophoretic devices, or sonophoretic devices.[55]

Chopra*et al.*developed a chronotherapeutic tablet for oral delivery of a drug within 24 hours comprising a substantially oblong core having a longitudinal axis, a first end and a second end, the core being comprised of at least two superposed layers of different compositions wherein an interface between each layer is substantially perpendicular to the longitudinal axis of the core and wherein at least one of the layers is a pharmacological composition. The formulation is able to release the drug within 15 minutes from the first layer, the second layer takes time between 5 to about 9 hours for complete dissolution and the third layer is then released within 15 minutes completely after complete dissolution of second layer. Author investigated the use of drugs selected from the groups consisting of a beta-2-adrenergic agonist, salbutamol sulphate, terbutaline sulphate, or systemic Xanthine, Aminophyllin, and Theophylline. Author also discussed methods for the prevention and/or treatment of asthma, osteoarthritis, rheumatoid arthritis, hypertension, angina, myocardial infarction, stroke and cancer.[56]

Карашуров*et al.,*developed a method of treating asthma. The method is based on a well-studied phenomenon that stimulation of the stellate ganglia leads to bronchodilation and inhibition of mucus secretion. The method consists of applying electrostimulation by using current frequency of 10 - 100 Hz, the voltage 1 - 3, the pulse duration of 0.1 - 0.3 ms, through implanted electrodes. Electrostimulation is carried out at the moment of an attack. Electrostimulation is set in action by applying radio frequency method in remote control mode. Stimulation current operation mode is tuned by means of corresponding control units in process of electrostimulation. Transmitting device is used for switching it in, corresponding to

particular patient needs. Automatic mode of stimulation control is carried out by means of programmed timer unit for switching stimulation modes on, being a part of transmitting device. Time of day and stimulation duration are programmed in advance by taking into account periodicity and duration of attacks in particular person. Authors conducted clinical trials on patients, in one of the trials patient suffered from bronchial asthma for 7 years and needed oral and intravenous medicine. Patient was treated using this and therapeutic electrostimulation was done for 2 minutes after every 4-5 hours. Current pulses of 100 Hz, 0.1 ms, 1 B were used. After 8 days of electrical stimulation the patient's condition began to improve. The number of attacks per day dropped to 5, and a after a month of starting treatment decreased to 3-4. The demand for drugs also decreased. Patient only had one short (about a week), exacerbation of the disease due to the worsening of bronchitis.[57]

Bhushan *et al.* formulated a press-coated tablet comprising a core of prednisone which is coated with either a hydrophilic or hydrophobic material. The hydrophilic material used can be hydroxypropyl cellulose, hydroxy propyl methyl cellulose, polyvinyl pyrrolidone, cross-linked polyacrylic acid, polyvinyl alcohol, carboxy methyl cellulose, methyl cellulose, hydroxyethyl cellulose, starch derivatives, hydrocolloids including alginate, chitosan, pectin, poly (ethylene oxide), carbopol, gums or their combination and hydrophobic material used can be glyceride stearic acid, hydrogenated vegetable oils, a water insoluble cellulose, a wax or a wax-like substance, a fat, an oil, a fatty acid, an emulsifier, a modified starch, a fatty alcohol, a protein, shellac, or a polymer (e.g., a polyolefin, a polyurethane, a polyvinylchloride, a polyvinyl acetate, an acrylic acid polymer, a methacrylic acid polymer); cetostearyl alcohol, stearyl alcohol or their combination. The lag time before the release of prednisone is from about 2 to about 3 hours upon administration to the patients and the tablet has to release 80% of the drug within 4 hours.[58]

Odidi *et al.* invented a controlled drug delivery composition for controlled release of an active ingredient that can be used for chronotherapy. The delivery system comprises a core comprising the active ingredient and at least two coatings substantially surrounding the core. The coatings comprise polymeric layers and wherein the polymers for each coating are applied separately and are pH insensitive polymers or a mixture of pH insensitive and pH sensitive polymers. The first coat comprises at least one layer of ethylcellulose, a second coat comprises at least one layer of methacrylate copolymer, and a third coat comprises at least one layer of polyvinyl acetate polymer.[59]

Chen*et al.* developed a unit dosage form which is capable of sequentially delivering drugs in a pulsatile manner. The system is a multiparticulate system comprising of coated pellets. The pellets comprise of a core containing drug and a swelling agent which is coated with an insoluble water permeable coating. As water diffuses into the core the core swells leading to bursting of the coating and releasing of the drug. The rate of ingress of water can be controlled by using permeability reducing agents causing a delaying action. The swelling agents that can be used are; cross-linked polyvinylpolypyrrolidone, cross-linked carboxymethylcellulose or sodium starch glycolate. The water-soluble film-forming polymer is selected from the group consisting of: cellulose acetate phthalate, cellulose acetate *etc*. and water insoluble polymer is selected from cellulose derivatives, acrylic resins or copolymers of acrylic acid.[60]

Conte*et al.* developed a tablet capable of delivering active agent in three pre-timed sequential pulses. The delivery system comprises of three layer; an outermost layer capable of immediate release of the active ingredient, second layer comprising of polymeric material suitable to form a barrier able to determine a time interval between the release of the active substance contained in the upper layer and the active substance contained in the lower third layer. The second retarding layer was formulated using hydroxypropylcellulose polymer and the first and third fast release layers were formulated using superdisintegrants and some effervescent salts such as citric acid or tartaric acid.[61]

Penhasi*et al.* formulated a two-pulse drug delivery device for delivering one or more active agents to the gastrointestinal tract of a subject. The device comprises of a core containing active ingredient and a swelling agent that is able to swell in presence of aqueous liquid. The core is coated with an inner release delaying coat and an outer

coat. The outer coat contains an active ingredient and a release controlling polysaccharide. When device comes in contact with aqueous fluid first the drug from the outer layer is released and after a delay the fluid reaches the core which swells and releases the active ingredient.[62]

Ting*et al.* invented a press-coated tablet suitable for oral administration, comprising of an inner immediate-release compartment containing blend of an active agent and one or more polymers. The inner layer has been press-coated with an outer extended release layer formulated using blend of hydrophilic (carboxymethylcellulose, guar gum, hydroxyethyl cellulose etc.) and hydrophobic polymers (carbomer, carnauba wax, ethyl cellulose, glyceryl palmitostearate, hydrogenated castor oil). The developed delivery system is able to give a first order release after an initial immediate release.[63]

Davar*et al,* developed a sustained release dosage forms for orally administering a leukotriene-receptor antagonist at a controlled-rate over an extended time indicated for treating asthma. Leukotriene-receptor antagonist is selected from the group consisting of Acitazanolast, Iralukast, Montelukast, Pranlukast, Yelukast, Zafirlukast, and Zileuton. The delivery system comprises of a core containing an amorphous, crystalline monohydrate or crystalline anhydrous form of the active agent and a pharmaceutically acceptable carrier (carboxyalkylcellulose or polyethylene oxide) for transporting the leukotriene-receptor antagonist from the dosage form. The core is surrounded by water permeable and drug impermeable wall having an exit for the drug. Authors also described a dosage form that administers a sustained-release dose of Zafirlukast over twenty-four hours and thereby decreases the frequency of dosing and maintains the therapeutic effect of the Zafirlukast.[64]

CONCLUSION

Nocturnal Asthma is a life changing disease and impairment due to asthma can have a substantial impact on quality of life. As research, has shown that various diseases show rhythmicbehaviour in their symptom's and severity therefore the timing of treatment according to biological rhythm of disease has a significant benefit over conventional therapy. Use of chronotherapy in management of nocturnal asthma has led to effective management of asthma.Many drugs used in management of asthma have been studied for chronotherapy and studies have shown that chronotherapy has considerable advantage over conventional treatment.Chronotherapeutic drug delivery systems have been formulated for chronotherapy using different strategies. Therefore, it can be concluded that this new field of research has a promising future.

REFERENCES

1. Katzung BG, Masters SB andTrevor AJ. Basic &Clinical Pharmacology Bertram.9th ed. McGraw-Hill Education;9th edition. 2003.
2. Smolensky MH.Chronobiology and chrono-therapeutics applications to cardiovascular medicine. AJH. 1996;(9)4:3:11s-21s.
3. Pittendrigh CS. Temporal organization: reflections of a Darwinian clock-watcher, Annu Rev Physiol.1993;55:16–54.
4. YouanBBC. Chronopharmaceutics: gimmick or clinically relevant approach to drug delivery? J Control Release. 2004;98:337–353.
5. Smolensky MH andD'Alonzo GE. Biologic rhythms and medicine. Am J Med. 1988; 85:34–46.
6. Reinberg A andSmolensky MH.Biologic rhythms and medicine, cellular, metabolic, pathophysiologic, and pharmacologic aspects. Springer-Verlag, Heidelberg. 1983: 305.
7. Haus E andTouitou Y: Biologic rhythms in clinical and laboratory medicine. Springer-Verlag, Heidelberg. 1992: 730.
8. Smolensky MH and Peppas NA. Chronobiology, drug delivery, and chronotherapeutics.Adv Drug Deliv Rev. 2007;59:828–851.
9. DaltonKD. The Premenstrual Syndrome, Charles Thomas, Springfield, IL. 1964.
10. Dardente H and Cermakian N. Review: Molecular circadian rhythms in central and peripheral clocks in mammals. Chronobiol Int.2007;24:195–214.
11. Duguay Dand Cermakian N. The crosstalk between physiology and circadian clock proteins. Chronobiol Int.2009;26:1479–1513.
12. Reinberg A: Clinical Chronopharmacology. an experimental basis for chronotherapy. In: Reinberg A, Smolensky MH, editors. Biologic rhythms and medicine, cellular, metabolic, pathophysiologic, and pharmacologic aspects. Springer, Heidelberg1983: 243–248.

13. Reinberg AE. Concepts of circadian chronopharmacology. In: Hrushesky WJM, Langer R, Theeuwes F, editors. Temporal control of drug delivery. Ann N Y Acad Sci.1991; 618:102–115.
14. Lemmer B. Chronopharmacology: cellular and biochemical interactions. Marcel Dekker, New York. 1989: 720.
15. Lemmer B. Chronopharmacology and controlled drug release. Expert Opin. Drug Deliv.2005;2:667–681.
16. Redfern PHandLemmer B. Physiology and Pharmacology of Biological Rhythms, Handbook of Experimental Pharmacology, vol. 125, Springer, Heidelberg. 1997.p. 668.
17. Bélanger PM. Chronopharmacology in drug research and therapy, Adv Drug Res. 1993;24:1–80.
18. Smolensky MH. Knowledge and attitudes of American physicians and public about medical chronobiology and chronotherapeutics. Findings of two 1996 Gallup surveys. Chronobiol Int.1998;15:377–394.
19. Wells BG, DiPiro JT, Schwinghammer TLand DiPiro CV. Pharmacotherapy Handbook, 7th ed. The McGraw-Hill Companies, Inc. 2009: 906.
20. Goodman, Gilman. The pharmacological basis of therapeutics. McGrawhill.11th ed. 2006.
21. Rang HP, Dale MM, Ritter JM and Moore PK.Text book of pharmacology. New York: Churchill Livingstone. 5th edition. 2000.
22. SmolenskyMH, Lemmer Band ReinbergAE. Chronobiology and chronotherapy of allergic rhinitis and bronchial asthma. Adv. Drug Deliv. Rev.2007; 59: 852–882.
23. Martin RJ. Nocturnal asthma: Understanding chronobiology and chronotherapy. Allergol Int. 1997;46:17-24.
24. Chen H, Gould MKand Blanc PD. Asthma control, severity, and quality of life: quantifying the effect of uncontrolled disease. J Allergy Clin Immunol. 2007;120:396–402.
25. The Global Initiative for Asthma (GINA) Report, Global Strategy for Asthma Management and Prevention, evidence-based guidelines for asthma management and prevention. Updated December 2008. Available from http://www.ginasthma.com/.Accessed 1 April2017.
26. Kikuchi Y, Okabe S, Tamura G, Hida W, Homma M, Shirato KandTakishima T.Chemosensitivity and perception of dyspnea in patients with a history of near-fatal asthma. N Engl J Med.1994;330:1329–1334.
27. Nainwal N. Chronotherapeutics - A chronopharmaceutical approach to drug delivery in the treatment of asthma. J Control Release.2012;163:353–360.
28. National Asthma Education and Prevention Program, Third Expert Panel on the Diagnosis and Management of Asthma.Bethesda (MD): National Heart, Lung, and Blood Institute (US); 2007 Aug. http://www.ncbi.nlm.nih.gov /books/NBK7232/ Accessed 1 April2017.
29. Castro Mand Kraft M. Clinical asthma,1st ed. Elsevier mosby. 2008: 367-370.
30. Durrington HJ, Farrow SNand Ray DW.Recent advances in chronotherapy for the management of asthma. ChronoPhysiology and Therapy. 2014;4:125–135.
31. Maneechotesuwan K, Essilfie-Quaye Sand Meah S. Formoterol attenuates neutrophilic airway inflammation in asthma. Chest. 2005;128:1936–1942.
32. Twentyman OP, Finnerty JP, Harris A, Palmer Jand Holgate ST. Protection against allergen-induced asthma by salmeterol. Lancet.1990;336:1338–1342.
33. Postma DS, Koëter GH, Keyzer JJand Meurs H. Influence of slow-release terbutaline on the circadian variation of catecholamines, histamine, and lung function in nonallergic patients with partly reversible airflow obstruction. J Allergy Clin Immunol. 1986;77:471–477.
34. Koëter GH, Postma DS, Keyzer JJ. Meurs H: Effect of oral slow release Terbutaline on early morning dyspnoea. Eur J Clin Pharmacol. 1985;28:159–162.
35. Dahl R, Harving H, Säwedal Land Anehus S. Terbutaline sustained-release tablets in nocturnal asthma – a placebo-controlled comparison between a high and a low evening dose. Br J Dis Chest. 1988;82:237–241.
36. Arvidsson P, Larsson S, Löfdahl CG, Melander B, Svedmyr Nand Wåhlander L. Inhaled formoterol during one year in asthma: a comparison with salbutamol. Eur Respir J. 1991;4:1168–1173.
37. Kesten S, Chapman KRand Broder I. Sustained improvement in asthma with long-term use of

Formoterol Fumarate. Ann Allergy.1992;69:415–420.

38. Ball DI, Brittain RT and Coleman RA. Salmeterol, a novel, long-acting beta 2-adrenoceptor agonist: characterization of pharmacological activity in vitro and in vivo. Br J Pharmacol. 1991;104:665–67.

39. Peters SP, Kunselman SJand Icitovic N. National heart, lung, and blood institute asthma clinical research network. Tiotropium step-up therapy for adults with uncontrolled asthma. N Engl J Med. 2010;363:1715–1726.

40. Beam WR, Weiner DEand Martin RJ. Timing of Prednisolone and alteration of airways inflammation in nocturnal asthma. Am Rev Respir Dis. 1992;146:1524-1530.

41. Pincus DJ, Szefler SJ, Ackerson LMandMartin RJ. Chronotherapy of asthma with inhaled steroids: the effect of dosage timing on drug efficacy. J Allergy Clin Immunol. 1995;95:1172–1178.

42. Pincus DJ, Humeston TRand Martin RJ. Further studies on the chronotherapy of asthma with inhaled steroids: the effect of dosage timing on drug efficacy. J Allergy Clin Immunol.1997;100:771–774.

43. Buhl R, Vinkler Iand Maygar P. Comparable efficacy of ciclesonide once daily versus fluticasone propionate twice daily in asthma. Pulm Pharmacol Ther. 2005;19:404–412.

44. Kidney JC, Dominguez M, Taylor PM, Rose M, Chung KFandBarnes PJ.Immunomodulation by Theophylline in asthma. Demonstration by withdrawing of therapy. Am J Respir Care Med. 1995;151:1907–1914.

45. Sullivan P, Songul B, Jaffar Z, Page C, Jeffery Pand Costello J. Antiinflammatory effects of low dose oral Theophylline in atopic asthma. Lancet. 1994;343:1006–1008.

46. Darow Pand Steinijans VW. Therapeutic advantage of unequal dosing of Theophylline in patients with nocturnal asthma. Chronobiol Int. 1987;4:349–357.

47. D'Alonzo GE, Smolensky MHand Feldman S.Twenty-four hour lung function in adult patients with asthma. Chronoptimized theophylline therapy once-daily dosing in the evening versus conventional twice-daily dosing. Am Rev Respir Dis. 1990;142:84–90.

48. Kemp JP. Recent advances in the management of asthma using leukotriene modifiers. Am J Respir Med. 2003;2:139–156.

49. Drazen JM, Israel Eand O'Byrne PM. Treatment of asthma with drugs modifying the leukotrien pathway. N Engl J Med. 1999;340:197–206.

50. Noonan MJ, Chervinsky Pand Brandon PM. Montelukast, a potent leukotriene receptor antagonist, causes dose-related improvements in chronic asthma. Montelukast Asthma Study Group. Eur Respir J. 1998;11:1232–1239.

51. Mandal AS, Biswas N, Karim KM, Guha A, Chatterjee S, Behera Mand Kuotsu K.Drug delivery system based on chronobiology-A Review. J Control Release. 2010;147(3):314-325.

52. Maroni A, Zema L, Del Curto MD, Loreti Gand Gazzaniga A. Oral pulsatile delivery: Rationale and chronopharmaceutical formulations. International Journal of Pharmaceutics. 2010;398:1–8.

53. Maroni A, Zema, L, Cerea Mand Sangalli ME. Oral pulsatile drug delivery systems. Expert Opin Drug Deliv. 2005;2:855–871.

54. Baichwal AR. Chronotherapeutic dosage forms and methods of treatment using chronotherapy. US 200300822.30A1. 2003.

55. Dipierro G. Biosynchronous transdermal drug delivery for longevity. Anti-aging, fatigue management, obesity, weight loss, weight management, delivery of nutraceuticals, and the treatment of hyperglycemia, alzheimer's disease, sleep disorders, parkinson's disease, aids, epilepsy, attention deficit disorder, nicotine addiction, cancer, headache and pain control, asthma, angina, hypertension, depression, cold, flu and the like. US 20080220092A1. 2008.

56. Chopra S. Chronotherapy tablet and methods related thereto. US20040137062A1. 2004.

57. Карашуров СЕ. Method for treating the cases of bronchial asthma.RU2108817C1.1998.

58. Bhushan Roy S. Press-coated tablets of prednisone.US20130243861A1.2013.

59. Odidi I, Odidi A. Controlled release delivery device. CA2579382C.2007.

60. Anda SR Pharmaceuticals, Inc. Pulsatile particles drug delivery system. US5260069; 1993.

61. Jagotec AG. Pharmaceutical tablet suitable to deliver the active substance in subsequent and predeterminable times.US6294200; 2001.

62. Dexcel Pharma Technologies Ltd. Delayed total release two pulse gastrointestinal drug delivery system.US6632451; 2003.

63. Impax Pharmaceuticals, Inc.Press coated pulsatile drug delivery system suitable for oral administration. US6372254; 2002.

64. Alza Corporation.Anti-asthma therapy.US6224 907 B1.2001.