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Chronotherapeutics drug delivery system: A promising approach to treat hypertension

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ABSTRACT

The circadian rhythm of mammals exists in the suprachiasmatic nuclei (SCN) and influences an assembly of biological processes, including the sleep-wake rhythm. Clock cycles are the genes that control the circadian rhythms in physiology and behavior of the mammals. Circadian rhythm has been proved for the function of physiology and the pathophysiology of diseases. The effectiveness and adverse toxicity of many drugs vary depending on dosing time. The Novel technology for delivering medications surely in a time-dependent is being developed to manage certain diseases. Chronopharmaceutics is a branch of pharmaceutics keen to the design and evaluation ofdrug delivery system that release a active pharmaceutical agent at a rhythm that preferably matches in realtime for the biological requirement of a given disease therapy.

Keywords: Circadian rhythm, Chronobiology, Hypertension, SCN, Chronopharmaceutics, Biological clock, chrono pharmacology, Chrono therapeutics, Melatonin.

INTRODUCTION

Chronobiology is "the study of biological rhythms and their mechanisms. Biological rhythms are defined by the number of characteristics"[1]. The term ''circadian'' was coined by Franz Halberg from the Latin circa, meaning about, and dies, meaning day[2]. Oscillations of shorter duration are termed as''ultradian'' (more than one cycle per 24 h). Oscillations that are longer than 24 h are termed ''infradian'' (less than one cycle per 24 h) rhythms. Ultradian, circadian, and infradian rhythms coexist in almost all levels of biologic organization[1].Chronobiology is a flourishing research field whichincludes all biomedical disciplines, from molecular biology and metabolism to psychology and internal medicine. Circadian rhythms are created at the molecular level in about all cells of the body. This group of clocks forms the "circadian system" that manages every feature of our biology daily—from the cells, tissues and organs up to the in-depth regulation of

metabolism or higher functions like sleep wake activities, cognition or immune responses.The mammalian circadian rhythm is actively harmonized to light and dark cycle with the help of a 'master clock' in our brain. Industrialization and urbanization have markedly changed the way we are exposed to light and darkness, and consequently how our clocks synchronize. The modern syndrome of social jetlag, which is a mismatch between social time and circadian, is a consequence of this. In most of us, the circadian clock is so delayed that we must interrupt with our natural sleep with an alarm clock to be awake for school/work schedules. Shift labors suffer from the higher-risk form of social jetlag.

Growing bodies of studies shows that this misalignment is associated with health shortfalls, including various metabolic, psychiatric and cardiovascularconditions and even increased risk of cancer[3]. All photosensitive organisms have a biological clock to cope with earth's daily and seasonal circle. Biological clocks create circadian rhythms and control their processing according to world's cycle. The adaptation of the living organisms to environment is the important purpose of the biological clocks. Circadian rhythms denote to changes in the organism's almostone day's biological, biochemical and physiological processes. In molecular level, there are thousands of biological clocks in the human body. The main clocks in the human brain systematize all these cellular clocks. Thus, the rhythmical phenomenon works in a harmony with both the master clock and solar cycle.

However, the natural factors present within the body produce circadian rhythms and the environment signals also affect them. The light is the primesignal that affects biological rhythm. These light–dark cycles can control the molecular structure of biological clocks. Altering the light–dark cycles leads toshorten, lengthen or complete absence of circadian rhythms. Dysfunction of circadian cycle leads to diverse health issues. The studies in chronobiology provide better understanding of the rhythmic metabolism and disrupted circadian rhythms[4].Aging is generally associated with weakening of the circadian system. The circadian amplitude when decreased, the circadian acrophase becomes more liable to change, tending to happen earlier with advancing age. As originally noted by Franz Halberg, similar features are witnessed in the experimental laboratory after bilateral lesioning of the suprachiasmatic nuclei, suggestive of the involvement of clock genes in the aging process as they are in various disease conditions. Recent works has been throwing light on the principal pathways involved in the aging process, with the promise of interventions to lengthen healthy life spans. Caloric restriction, which is consistently and reproducibly associated with prolonging life in different animal models, is associated with increased circadian amplitude. These indicate the importance of chronobiology in dealing with problems of aging, from the circadian clock machinery orchestrating metabolism to the development of geroprotectors.Chronobiologic facts, concepts, and methods are applicable to gerontology and geriatrics. Reference values accounting for rhythms and for changes with gender and age offer new sensitive endpoints as gauges of health and indicators for disease and predisease, making it possible to distinguish the presence of an increased disease risk from healthy aging. Effects of interventions such as caloric restriction or any other new geroprotector are readily assessed on an individual or population basis by a chronobiologic interpretation of longitudinal data from physiological monitors. Tracking physiological changes as a function of time helps health maintenance and even health improvement, thus 'adding life to years' and not just 'years to life'[5].

MELATONIN AND BIOLOGICAL CLOCK

Melatonin,ahormone secreted by the pineal gland, secreted at night in all species which is associated with sleep, lowered core body temperature and other nighttime events and thusconcerned with biological timing. The prime function of the 'biological night', a period of secretion of melatonin, is to 'transduce' information about the length of the nighttime, for the organization of day-length dependent changes, such as reproductive competence.Exogenous melatonin has acute sleepiness-inducing and temperature-lowering effects during 'biological daytime', and when suitably timed (it is most effective around dusk and dawn) it will shift the phase of the human circadian clock (sleep, endogenous melatonin, core body temperature, cortisol) to earlier (advance phase shift) or later (delay phase shift) times. The shifts induced are sufficient to synchronize to 24 h most blind subjects suffering from non-24 h sleep–wake

disorder, with consequent benefits for sleep. Successful use of melatonin's chronobiotic properties has been reported in other sleep disorders associated with abnormal timing of the circadian system: jetlag, shiftwork, delayed sleep phase syndrome, some sleep problems of the elderly.Although melatonin appears to be well tolerated and an effective treatment for a number of sleep disorders related to circadian rhythm disturbance, it is possible that more effective melatonin analogues will emerge, with proper safety and efficacy assessments. In the meantime, many countries (but not the USA) regard it as a drug requiring registration. A priority is to make melatonin available on prescription as a registered medication in these countries[6].

GENES OF CIRCADIAN BIOLOGY

Several genes have been identified in operation of biological clocks. In recent years, researchers have been focused on describing and analyzing clock gene expression[7-9]. It has been reported that one-third of all gene activity is regulated by the biological clock[7]. The circadian light receptors are encoded by the essential elements called crypto chromes (crypto chromic genes, CRY1 and CRY2). It has been accepted by the researches that crypto chromes play a fundamental role and they are the most important part of the circadian rhythm. In recent years, scientists defined myriad genes that govern circadian clocks such as BMAL1, CLOCK, CRY, PER, and TIM (specifically identified for the sleep process). It has been shown that these genes were found within the cells of nearly all body tissues but particularly active within the suprachiasmatic nuclei[10, 11]. The clock proteins which encoded by these genes in the human body could control the activity of these genes. Clock gene is the first identified gene[12, 13]. King et al. have identified BMAL1 gene (1997).BMAL1 gene is accepted as the heterodimer partner of CLOCK gene. So CLOCK-BMAL1 accepted as transcriptional activator complex[14]. Takahashi defined Period and Crypto chrome genes. [15] In 2002, it was defined "core circadian clock genes" (BMAL1, CLOCK, CRY1, CRY2, PER1, PER2)[16]. In the periodicity of the circadian rhythm, it has been found to be important of the regulation of the stability of the PER and CRY proteins by specific E3 ubiquitin ligase complexes[8, 10, 11, and 17]. All these models describe the circadian clock in mammals. Increased recognition of the responsible genes in the circadian rhythm also provides an understandable processing mechanism of the human body. It has been known that the human body possesses internal time regulators which are genetically determined. Consequently, it is well known that a genetically manifested clock in the human body governs fundamental rhythmicity and enables homeostasis of the organism. It is clearly understood that the circadian rhythmicity is responsible for physiological, biological, and biochemical integrity of the human body. However, it is still unclear that how does circadian rhythmicity integrate with the physiologic systems. Although the numerous genes have been defined in process of the biological rhythmicity, the genetic and molecular mechanisms of circadian clocks also remain unclear. Learning more about the responsible genes for circadian rhythmicity will also help us to comprehend biological patterns of the human body.

Melatonin modulates circadian rhythms in physiology and sleep initiation. Genetic variants of the MTNR1B locus, encoding the melatonin MT2 receptor, have been associated with increased type 2 diabetes (T2D) risk. Carriers of the common intronic MTNR1B rs10830963 T2D risk variant have modified sleep and circadian traits such as changes of the melatonin profile. However, it is currently unknown whether rare variants in the MT2 coding region are also associated with altered sleep and circadian phenotypes, including meal timing. In this pilot study, 28 individuals [50% male; 46–82 years old; 50% with rare MT2 mutations (T2D MT2)] wore actigraphy devices and filled out daily food logs for 4 weeks. We computed circadian, sleep, and caloric intake phenotypes, including sleep duration, timing, and regularity [assessed by the Sleep Regularity Index (SRI)]; composite phase deviations (CPD) as well a sleep timing-based proxy for circadian misalignment; and caloric intake patterns throughout the day. Using regression analyses, we estimated age- and sex-adjusted mean differences and 95% confidence intervals between the two patient groups. Secondary analyses also compare T2D MT2 to 15 healthy controls. Patients with rare MT2 mutations had a later sleep onset, and midsleep time, slept more irregularly had higher levels of behavioral circadian misalignment were

more variable in regard to duration between first caloric intake and average sleep offset and had more caloric episodes in a 24 h day in comparison to T2D controls. Secondary analyses showed similar patterns between T2D MT2 and non-diabetic controls. This pilot study suggests that compared to diabetic controls, T2D MT2 patients display a number of adverse sleep, circadian and caloric intake phenotypes, including more irregular behavioral timing. A prospective study is needed to determine the role of these behavioral phenotypes in T2D onset and severity, especially in view of rare MT2 mutations[18].

Disruption of circadian rhythms, such as that due to shift work, affects not only body weight and adiposity, but glucose metabolism itself. Since the magnitude of these effects in the present increase seen in the development of type 2 diabetes is obscure, more precise mechanisms and the relative importance of these factors in the development of type 2 diabetes should be investigated. To achieve this goal, it will be necessary to establish methodologies to measure parameters of circadian systems in feeding and glucose and lipid metabolism[19]. In addition, it is also necessary to analyze the contribution of circadian gene variations in the development of type 2 diabetes. Clinical studies related to the development of type 2 diabetes are also needed to evaluate the health-compromising behaviors that affect circadian dis-ruption with definitions that include chronotype or circadian typology[20].

CHRONOPHARMACOLOGY

The circadian clock acts like a multifunction timer to control homeostatic systems such as sleep and activity, appetite, hormone levels, and other bodily functions with 24 h cycles. Not just the physiology, but also the pathophysiology is impacted by the biological rhythms. Chronopharmacology is the investigative science that detailing the biological rhythm dependencies of medications. The efficacy and toxicity of many drugs vary depending on dosing time associated with 24 h rhythms of behavioral, biochemical and physiological processes under the control of circadian clock. Such chronopharmacological phenomena are influenced by both pharmacodynamics and pharmacokinetics of medications. The knowledge of circadian rhythm in the disease risk and evidence of circadian rhythm dependencies of drug pharmacokinetics, effects, and safety constitutes the rationale for chronotherapy. Chronotherapy is peculiarly relevant in the conditions where the risk and/or intensity of the symptoms of diseases vary predictably, as in allergic rhinitis, arthritis, asthma, congestive cardiac failure, stroke, myocardial infarction, peptic ulcer, etc. Since many drugs vary in potency and/or toxicity associated with the rhythmicity of biochemical, physiological and behavioral processes, the intra-individual variability as well as inter-individual variability should be considered to aim at further improvement of rational pharmacotherapy.According to pharmaceutical views, appropriate timing of conventionally formulated tablets and capsules can help to relate biological rhythm to pharmacotherapy. Likely, the special drug delivery system can be transformed to synchronize drug concentrations to rhythms in disease activity. “New technology for delivering medications precisely in a time-modulated fashion by bedside or ambulatory pumps is developing to manage human diseases” [21].

Many pathophysiological circumstances fluctuate during 24 h periods. Many physiologic processes undergo biological rhythms, including the sleep–wake rhythm and metabolism. Chronotherapeutics is gaining increasing interest in medicine, experimental biology, pharmacy and drug delivery, as the disrupting effect in the rhythmic variations can manifest as emergence or exacerbation of the pathologic conditions. This science and the abundant information should be used logically for optimizing the efficiency and safety of the drug, depending on the timing of drug intake. Both the pharmacodynamics and the pharmacokinetics of the drugs affects their Chronopharmacologyisis.The mammalian circadian pacemaker is located in the suprachiasmatic nucleus. The molecular mechanisms are associated with *Clock* genes that control the circadian rhythms in physiology, pathology and behavior. *Clock* controls several diseases such as metabolic syndrome, cancer, and so on. CLOCK mutation influences the expression of both rhythmic and non-rhythmic genes in wild-type tissues. These genotypic changes lead to phenotypic changes, affecting the drug pharmacokinetic and pharmacodynamics parameters [22].

*Chronopharmacology*is thus the study of impact of the administration time of a drug (hour, month, and year) on its response according to the temporal structure of the organism receiving it[23].“Two aspects of chronopharmacological must be distinguished: the time of administration of a drug may determine a different response from a qualitative or a quantitative point of view (chronopharmacodynamics) and/or a different effective drug concentration (chronopharmacokinetics)” [24, 25].

CHRONOTHERAPY

Considering the circadian rhythms for medical treatment by selecting the time of day for drug administration is called *chronotherapy*. Based on drug administration on the circadian pattern of the disease can help decreasethe side effects and optimize the drug effects.

CHRONOPHARMACOTHERAPY FOR EPILEPSY

Epilepsy is the most severe neurological condition that affects individuals of all ages[26, 27]. An estimated 50 million people have been diagnosed with epilepsy worldwide, and the incidence is 16–51 new cases per 100,000/year. Despite the increased use of anti-seizure drugs (ASD), drug-resistant epilepsy (DRE) remains uncontrolled in a third of patients. DRE often persists even after treatment with two or more drugs[28]. DRE is linked with a poor quality of life, and a high risk of sudden, unexplained death[29].

Cyclic rhythms control epilepsy, with increasing seizure rates and dropping intermittently, over periods of weeks, months, or years. Most epilepsy is subject to some diurnal influence[30]. Patients with frontal lobe-type epilepsy have more seizures during sleep than those with temporal lobe epilepsy (TLE)[31].Various studies performed to identify the influence of circadian rhythm in the occurrence of epilepsy explained that seizures occurred highly in the periods 08:01 – 12:00 and 16:01 – 20:00 implying that there were circadian modulations in the seizure rates. Similar studies showed that, some subjects manifested strong circaseptan rhythms, with a seven-dayperiod[32, 33]. The interictal epileptiform activity (IEA) that is the brain irritability marker was also observed among seizures, thus substantiating their association. Further studies showed that, IEA oscillated with circadian and subject specific multi-day periodicities, mostly 20-30 days, and seizures occurred especially during the rising phase of multidien IEA rhythms[34].

Seizures can follow a 24 –h non-random or non-uniform shape. In a study of 544 seizures in 123 consecutive subjects, the seizure-specific times were spread along 3- or 4 -h time blocks during a 24 -h period. Non-uniform distribution of seizures was noted in temporal lobe epilepsy, showing two peaks found in both 3- and 4 -h periods. However, as peak times vary between studies, rhythmic exogenous triggers or environmental/social “zeitgebers” may modulate the 24 -h rhythmicity of seizures[35]. Generalized seizures occur most frequently out of sleep and in older patients. A study performed on 71 epileptic patients with a total of 223 seizures, it was observed that sleep/wake seizure spreading better predicted tonic-clonic seizure, and that more seizures occurred during sleep, more frequent between 00:00-03:00 and 06:00-09:00[36]. Tonic-clonic seizures are ASD and the use of other medications also modifies the sleep patterns of people with epilepsy[37].

The potential role of chronobiology in epilepsy projected as a basis for the development of chronotherapy-based modalities, which may have some benefit in DRE. Chronopharmacologyis, differential medication dosing, chronopharmaceutical delivery methods, and utilization of zeitgebers, including chronobiotics or light-therapy and desynchronization, have been suggested[38]. The three features of chronopharmacological are the pharmacokinetics of the drug and its relation to circadian rhythms, the chronobiology of disease, and the interaction between biological rhythms and pharmaceutical action. Customization to a patient’s phonotype cans helpchronotherapy and chronopharmacological. These can be evaluated by questionnaires like Morningness Eveningness questionnaire (MEQ) orby direct measurements of dim lightmelatonin onset (DLMO), cortisol production, actigraphic factors, and sleep parameters[39].Valproic acidshows 24 h variation in absorption, distribution and excretion[40-42]. Volunteers who received continuous infusion of Midazolam were found to exhibit slightly higher levels of drugs at nighttime

[43]. Increased levels of diazepam were found in morning rather than the evening dose in healthy volunteers administered with bis in die doses of Diazepam. Healthy volunteers receiving bi-daily doses of diazepam showed elevated levels of diazepam[44, 45].

Melatonin is related with the control of circadian rhythm and exerts ananti-seizure and neuroprotective effect. In a model of TLE, melatonin improved the seizure-latent period, reduced the incidence of spontaneous recurrent seizures (SRSs), and decreased the circadian rhythm of seizures. Melatonin decreased neuronal damage in the hippocampus and piriform cortex. Agomelatine, an anti-depressant, functions as an agonist to melatonin MT1 and MT2 receptors, and as an antagonist to the serotonin 5HT2C receptor. It also reduces the depolarization-evoked release of glutamate, induces a neuroprotective action, and has been proposed as a treatment for epilepsy.Differential dosing based on the 24 -h seizure rhythm can improve treatment effectiveness while reducing adverse reactions.

Some ASDs have side effects that also have 24h rhythmicity, so differential dosing can help preven t or decrease these side effects[46].

CHRONOPHARMACOTHERAPY FOR TUBERCULOSIS

Several factors have been assigned to the relationship between chronobiology and TB. For this partnership, the most important factors are discussed here. Photosynthesis produces over 90% of the bioavailable vitamin D, although other sources are also significant[47, 48]. This vitamin can be acquired, in both D2 and D3 types, from vegetable and animal sources in the diet. It is important to remember that vitamin D dietary intake is not subject to seasonal variation. It is also possible to maintain regular serum levels of vitamin D even in environments with adverse sunshine, photoperiod, and temperature conditions[49], hiding the connection between TB and chronobiology. The hypothetical impact of winter conditions on the occurrence of symptoms of TB can be applied to primary infection and re-infection, but there are no circumstantial lymphocyte function oscillations. [49, 50] There are also studies that have speculated on the relationship between TB and other variables, such as photoperiods, [50] latitude[51, 52] and insolation or radiation[51-53]. In this context, it should be noted that chronobiological tuberculosis variations can be synchronized mainly by the infrared cycle (seasonality, photoperiod and radiation), but also by the circadian cycles (radiation). It remains overlooked, however, in spite of the possible importance of the proposed partnership. Chronobiological methods are, therefore, seldom applicable to TB-related health policies.

CHRONOPHARMACOTHERAPY FOR CARDIAC DISEASES

Circadian rhythms are subject to many functions (e.g. BP, heart rate, stroke volume, cardiac production, blood flow) of the cardiovascular system. Capillary resistance and vascular reactivity, for instance, are greater in the morning and decrease later in the day. In the morning, platelet aggregation is increased and fibrinolytic activity is reduced, leading to a state of relative hypercoagulability of the blood[54-56]. Modification by pharmacological agents of these circadian causes has been postulated to avoid adverse cardiac events[56, 57]. Cardiac events also happen with a circadian design. Several studies have shown a rise in the occurrence of early-morning myocardial infarction, sudden cardiac death, stroke, and episodes of ischemia [57]. The circadian pattern of hypertension has been well recognized[58, 59]. Blood Pressure is at its least during the sleep cycle and rises steeply during the early morning awakening period. Most patients with essential hypertension have a similar circadian rhythm of BP as do normotensive persons, although hypertensive patients have an ascending shift in the contour [59].

CHRONOPHARMACEUTICS

In this context, it should be noted that chronobiological tuberculosis variations can be synchronized mainly by the infrared cycle (seasonality, photoperiod and radiation), but also by the circadian cycles (radiation). It remains overlooked, however, considering the possible importance of the proposed partnership. Chronobiological methods, in particular, are seldom applied to TB-related health policies. Ideally, time-controlled and site-specific drug delivery systems can embody chronopharmaceutical drug delivery systems

(ChrDDS)[54]. The advantages of chronobiology and chronopharmacology, system biology and Nano medicine[55], are safer, more powerful and effective therapeutic results[56].

Chronopharmaceutics will undoubtedly improve patient outcomes and optimize the treatment of diseases in the future. The key disadvantages of the current oral ChrDDS on the market are that, for example, they rely on human activity to cause drug administration on a daily basis. If taken at any time of the day, the optimal ChrDDS should be self-regulating and should take environmental variables into account (e.g. awake– sleep, light–dark, activity–rest status). Chronopharmaceutics' ultimate performance would rely on the efficient application of information from future advancements in timing of growth, system biology and Nano medicine. The application spectrum (e.g. targeted drugs of various physico-chemical properties), ease of processing, cost-effectiveness and versatility of the pharmacokinetic profile should be taken into account when choosing the required chronopharmaceutical technology.

A multiple pulse drug delivery system differs from single chronotherapeutics pulse delivery in the number of pulses delivered concurrently with the conforming number of lags. The first pulse is an immediate release pulse that begins to dissolve in the stomach. The subsequent pulses may be designed to provide a lag time followed by rapid release/delayed release pulses, which may be formulated using sustained or controlled release polymers, depending on the solubility of the drug or the dissolution properties of the core. The in house developed formulation successfully demonstrated provision of a two-fraction release of amoxicillin separated by a well-defined time-controlled lag phase.

The compression coating inlay tablet approach was used to deliver the drug in two pulses to different parts of the GIT after a well-defined lag time between the two releases. This was made possible by formulating a core containing one of the two drug fractions (intended to be delivered as the second pulse), which was spray coated with a suspension of ethyl cellulose and a hydrophilic but water insoluble agent as a pore former (microcrystalline cellulose). Coating of up to 5 % (m/m) was applied over the core tablet, giving a corresponding lag of 3, 5, 7 and 12 h. increasing the level of coating led to retardation of the water uptake capacity of the core, leading to prolongation of the lag time. Microcrystalline cellulose was used as a hydrophilic but water insoluble porosity modifier in the barrier layer, varying the concentration of which had a significant effect on shortening or elongation of the lag time. This coated system was further partially compression coated with the remaining drug fraction (to be released as the first immediate release pulse) with a disintegrant, giving a final tablet. The core tablet and the final two pulse inlay tablet were further investigated for their in vitro performance.

A two-pulse tablet consisting of a coated core tablet (inner layer) having the compression coating drug (outer layer) of well-defined lag time with controlled drug release was developed. This delivery system is proposed to counter the serious problem of bacterial resistance against antibiotics. Such type of release in spurts has proved to be more effective in successfully exterminating the microbes with a comparatively low dose compared to the conventional dosage regimens[57].

RESEARCHES ON CHRONOPHARMACEUTICAL DRUG DELIVERY SYSTEM

A study conducted by Malpuse tried and formulated a new oral chronopharmaceutical drug delivery system for asthma by using press-coating technology, with core tablet containing Montelukast sodium as the model drug and different natural gums making up the outer shell. Tablets press coated with various ratios of Xanthum gum and Locust bean gum underwent different tests which explain that drug release pattern changed with change in the coating composition, and such tablets showed acid resistance and timed-release functions[58].

In a research performed by Anil Kumar S. N. a colon specific, pulsatile drug releasing devise for Trimetazidine HCl was developed to attain time and site-specific release of the drug. The design consisted of sodium alginate microspheres of Trimetazidine filled in insoluble hard gelatin capsule sealed with a hydrogel plug and finally enteric coated to overcome the variability in the gastric emptying time and achieve colon-specific release. Upon evaluation, it showed that the proportion of polymers used controlled the drug release and that trimetazidine microsphere could be successfully targeted to colon by design of time

dependent and polysaccharide based chronopharmaceutical formulation[59].

For antihypertensive drugs with adequate amounts of excipients, a multiparticulate formulation pulsatile release system was created. In further studies, the impact of the type and quantity of super disintegrants and the type and concentration of polymer on the percentage of drug release of pulsatile formulation were studied. The optimized formulation consisted of 4% sodium starch glycolate and different concentrations of pH sensitive polymers, Eudragit – L100 and Eudragit – S100 and which successfully resulted in the lag time of 5 h followed by rapid release of drug, consistent with the demand of the chronotherapeutics drug delivery and increasing bioavailability[60].

Foppoli conducted an investigational research intending to incorporate Sternzym C13030 into systems designed for colon targeting or time-controlled release of drugs which opened new perspectives in the application of a technique allowing cellulosic coatings rather than organic or aqueous solvents. The study created a breakthrough not only by pointing out the fact that cellulose has release modulating activity but also by suggesting that coupling diverse release controlling polysaccharide agents with related hydrolytic enzymes[61].

Mcconville, performed photoscintigraphy study to establish the importance of an erodible hypomellose (HPMC) tablets in controlling the onset of pulsed release in vitro. The study concluded that the time delayed capsule performs and demonstrates an in vitro–in vivo correlation[62].

Sateesh Kumar Vemula conducted a research to analyse the effect of double-compression coated tablets prepared based on time-controlled hydroxypropyl methylcellulose K100M inner compression coat and pH-sensitive Eudragit S100 outer compression coat on ketorolac promethazine mini-tablets to attain the chronopharmaceutical delivery to colon. The study explained that the development of double-compression coated tablets was a promising way to acquire the chronopharmaceutical delivery of ketorolac tromethamine to colon[63].

CONCLUSION

Chronopharmaceutical drug delivery systems have the potential to transform the current drug delivery systems to the advantage of many patients, for eg., improve the medication adherence and thereby improve the treatment outcome[64-69]. The concepts of Chronobiology, Chronopharmacologyis and Chronopharmaceutical drug delivery systems are ages old, but still lack popularity due to the less number of studies related to this field. Thus there is scope for further research studies in the field of chronopharmaceutics.

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