

CHRONOTHERAPY: CURRENT STATUS AND FUTURE PROSPECTIVES

Ravi Sharma^{1*}, Gagan Sharma², Ashish Agrawal³ Shailendra Wadhwa³

1. Choksi Laboratories Limited, Manoramaganj, INDORE- 452001(MP),INDIA.
2. SVKM'S, NMIMS, SPTM, Shirpur Campus, Maharashtra, INDIA.

3. Mandsaur Institute of Pharmacy, Mandsaur, (MP) INDIA

Summary

Cell physiology is regulated along the 24 hours time scale by circadian rhythms composed of molecular clocks with in each cell and a central coordination system in the brain. The circadian rhythms are coordinated by the superchiasmatic nuclei, hypothalamic pacemaker who helps the organism to adjust the environmental cycles. These circadian rhythms are also responsible for predictable changes in the tolerability and the efficacy of drugs. This coordination of biological rhythms with medical treatment is called chronotherapy. Over the past few years, pharmaceutical industry has focused its research in the development of various chronotherapeutic delivery systems. By choosing the optimal time to achieve the desired effect, and treatment opportunities; undesirable side effects can be minimized. Due to this ability chronotherapeutics is the promising treatment for various diseases. Chronotherapy treatments for cancer, arthritis, asthma and hypertension are effective in present time. Researchers have strong hopes for great success, using chronotherapeutics for several life threatening diseases. This review article covers the effects of biorhythms on various disorders, and their implications for drug therapy.

Corresponding Author

Ashish Agrawal

MIP, Mandsaur (M.P.)

ashishpharma123@gmail.com

Introduction

Many of our body's internal processes are cyclical. There are daily patterns, like waking and sleeping; monthly patterns, like a woman's menstrual cycle, and even seasonal patterns, like those that cause seasonal affective disorder (SAD) during the winter months. But doctors are only recently beginning to understand these rhythms' impact on other conditions well enough to more effectively treat their patients.¹ The role of our body's biological rhythms also known as our biological clocks, in fighting disease has come under study. The idea that medical treatments can be improved based on, when they are given to a patient is called chronotherapy; which involves coordinating biological rhythms (chronobiology) with medical treatment.² It considers a person's biological rhythms in determining the timing and sometimes the amount of medication to optimize a drug's desired effects and minimize the undesired ones. By making use of this good timing, doctors are finding that they are able to treat more effectively a wide-range of diseases such as asthma, arthritis, diabetes and cancer, while reducing the side effects.³

Some of the rhythms that affect our bodies include:

- Ultradian: which are cycles shorter than a day (for example, the milliseconds it takes for a neuron to fire, or a 90-minute sleep cycle)
- Circadian: which last about 24 hours (such as sleeping and waking patterns)
- Infradian: referring to cycles longer than 24 hours (for example monthly menstruation)
- Seasonal: such as seasonal affective disorder (SAD), this causes depression in susceptible people during the short days of winter.

Drug Chronotherapy for the most part does not involve new medicines but using old ones differently: revising the dosing schedule, reformulating a drug so its release into the bloodstream is delayed, or using programmable pumps that deliver medicine at precise intervals are some of the simple changes that may reap enormous benefits. Chronomedicine can help you cope better with short-lasting illnesses such as colds and flu, episodic ones such as headaches and back pain and persistent ailments such as asthma, arthritis, diabetes, cancer and more.⁴⁻⁶

The 24 h clock pattern of diseases showing prominent day-night patterns when symptoms of disease are most frequent is shown in Fig. 1⁷.

OBJECTIVES

- Medical treatment administered according to a schedule that corresponds to a person's daily, monthly, seasonal, or yearly biological clock, in order to maximize the health benefits and minimize adverse effects.
- To deliver cancer treatments at specific times or according to specific chronomodulated schedules and/or specific drugs acting upon the time-keeping systems in order to improve therapeutic index.

Advantages of Chronotherapy^{3,10}

- It works rapidly and deliver drug when the symptom rate is high.
- Unlike other treatment, it has a beginning, middle, and an end. So it could be predicted when it will work.
- It gives a period to adjust psychologically to the new schedule. Whereas with Chronotherapy, the schedule becomes strange for a few days, then becomes more and more like normal.
- Chronotherapy is drug-free.
- Patient compliance is there with Chronotherapy.

Disadvantages of Chronotherapy

- Adjustment until the patients next scheduled can be uncomfortable.
- During chronotherapy, it will probably be less productive than usual.
- Patients will have to take time off from their normal routine, perhaps using their vacation time.
- The degree of risk is unknown.

CHRONOTHERAPY OF DISEASES

Chronotherapy of cancer

Finding new anticancer drugs and defining their optimal delivery schedule is the mainstay of developmental therapeutics. Chronotherapeutics aim to determine the most active treatment schedule, based on the adjustment of drug delivery to the 24-hour rhythms generated by the circadian timing system.^{8, 11-12} The suprachiasmatic nucleus (SCN) is a biologic clock located at the floor of the hypothalamus. It is able to maintain an approximate 24-hour cycle in its electrical activity *in vitro*. Its period (cycle duration) is calibrated by the alternation of light (L) directly and darkness (D) through melatonin secretion by the pineal gland.¹³⁻¹⁴

The SCN controls or coordinates the circadian rhythms in the body. The main circadian rhythm is the rest-activity cycle. Cellular metabolism and proliferation also display rhythms in normal tissues, which may be affected by the rest-activity cycle. Table 1 summarizes the main results published to date regarding human tumor circadian and ultradian rhythms.⁸

Mammalian cells contain a molecular clock with fine-tuned feedback loops of 12 specific genes.¹² This molecular clock regulates the cell division cycle, apoptosis, gene expression, and DNA repair, as well as several signaling and metabolic pathways. In the tumor, circadian regulation is mainly exerted at G2/M-phase, while BCL-2 expression is largely increased and lacks any rhythmicity.¹⁵ As a result, anticancer chemotherapy at specific circadian times can reduce toxicities for host cells and enhance efficacy against cancer cells.⁸

The treatment of cancer is usually scheduled by the convenience of the health care system. First, according to the availability of the clinical facilities and of the physician or nurse. Chemotherapy being usually highly toxic, the drug may cause harm to various organs, from the gut and kidney to the heart and/or bone marrow. Chronotherapy has been used to lower the amount of side effects from chemotherapy drugs. Over the years, doctors have realized that by giving two of these drugs, Adriamycin and cisplatin, in the morning and evening, respectively, side effects could be cut in half.¹⁶

Further understanding of the cancer cell cycle would be the next step. A few studies have shown that cancer cells function on a cycle independent of the rest of the body. Therefore, if researchers can pinpoint the best time to administer cancer-killing drugs, these treatments would be more effective and do less harm to the rest of the body. When cancer medications are given in a chronobiological manner, patients may be able to tolerate higher, more potent doses than would be possible otherwise.⁸

SCN, plays a key role in the coordination of circadian rhythms. This temporal organization makes it possible to predict the rhythmic aspects of cellular metabolism and proliferation. Synchronized individuals display circadian rhythms with predictable times of peak and trough. These rhythms may influence the pharmacology and the tolerability of anticancer drugs and/or their antitumor efficacy.¹⁷

Chronotherapy of asthma

Normal lung function undergoes circadian changes and reaches a low point in the early morning hours. This dip is particularly pronounced in people with asthma. Chronotherapy for asthma is aimed at getting maximal effect from bronchodilator medications during the early morning hours. One example is the bronchodilator Uniphyl, a long-acting theophylline preparation manufactured by Purdue Frederick Co. of Norwalk, Conn., and approved by FDA in 1989. Taken once a day in the evening, Uniphyl causes theophylline blood levels to reach their peak and improve lung function during the difficult early morning hours. There are other bronchodilators that act similarly to address the early morning dip in lung function, but the manufacturers have not sought or received FDA approval for chronotherapeutic labeling.¹⁸⁻¹⁹

Chronotherapy of arthritis

Chronobiological patterns have been observed with arthritis pain. People with osteoarthritis; the most common form of the disease, tend to have less pain in the morning and more at night. But for people with rheumatoid arthritis, the pain usually peaks in the morning and decreases as the day wears on. Recent animal studies showing that joint inflammation in rats fluctuates over a 24-hour period support these observations by both patients and physicians.²⁰⁻²¹

Chronotherapy for all forms of arthritis uses standard treatment, no steroidal anti-inflammatory drugs and corticosteroids; however, the dosages are timed to ensure that the highest blood levels of the drug coincide with peak pain.

For osteoarthritis sufferers, the optimal time for a nonsteroidal anti-inflammatory drug such as ibuprofen would be around noon or mid-afternoon. The same drug would be more effective for

people with rheumatoid arthritis when taken after the evening meal. The exact dose would depend on the severity of the patient's pain and his or her individual physiology.²²⁻²³

A major objective of chronotherapy is to deliver the drug in higher concentrations during the time of greatest need and in lower concentrations when the need is less. A circadian rhythm release (CRR) dosage form for a cardiovascular drug, propranolol hydrochloride, with a four-hour delay in release after oral administration has also been developed. Administered at bedtime, propranolol is released after the initial delay such that maximum plasma level occurs in the early morning hours, when the patient is most at risk H2-Receptor Antagonist: Certain gastrointestinal disease states exhibit circadian rhythm profiles. In particular, gastric acid refluxes.²⁴⁻²⁵

Chronotherapy of diabetes

The most widespread application of chronotherapy is insulin pump, which is used to administer insulin for the treatment of diabetes mellitus. With the insulin pump, patients can customize insulin delivery to meet their particular requirements.

Several systems were developed to respond the change in glucose concentration like pH sensitive hydrogel containing glucose-oxidase enzyme immobilized in hydrogel. As the blood concentration of glucose rises, glucose-oxidase converts glucose into gluconic acid, which changes the pH of system. Due to change in pH, swelling of polymer takes place and this result into insulin release. Insulin decreases the blood glucose level and consequently the gluconic acid level also declines and system turns to deswelling and hence decreasing the insulin release.²⁶

Chronotherapy of cardiac diseases

The chronobiological approach to physiology evaluates time-dependent changes in biological functions and considers those changes to be multifactorial. Chronotherapeutic approach gives more accurate determination of the time when patients are at highest risk and in greatest need of therapy. Circadian variations can occur due to myocardial ischemia, acute myocardial infarction, ventricular tachycardia, and sudden cardiac death. Factors affecting circadian variations in cardiovascular disorders include physiological determinants, such as heart rate, catecholamine release, and platelet aggregation which themselves vary cyclically and exogenous factors, such as mental stress, anxiety, and physical activity. In chronotherapy, circadian variations in disease states and in the pharmacodynamic properties of drugs are exploited to improve prevention and treatment. Chronotherapeutic approach may be advantageous in thromboembolism, hypertension, stable exertional angina, variant angina, sustained ventricular tachycardia, and acute myocardial infarction.²⁷⁻²⁸

Chronotherapy of sleep disorders

The circadian rhythm is not an immutable rhythm; it can be controlled by certain factors such as light and darkness, social interaction, sleep-wake schedule, timing for taking meals, etc. In the international classification published in 1990, sleep rhythm disorders such as non 24 h sleep-wake syndrome and delayed sleep phase syndrome are grouped together as circadian rhythm sleep disorder and treated as dyssomnias (Table 2).²⁹

CHALLENGES WITH CHRONOTHERAPY

Challenges of using chronotherapy in treating patients with hypertension: One research shows that about three-quarters of untreated people with essential hypertension are dippers, while about 20% are non-dippers. There is another group among elderly patients with hypertension, the extreme dippers, whose systolic blood pressure drops more than 20% below its daytime level. While some studies have linked this extreme dipping to end-organ damage, including white matter changes and silent cerebral infarcts, as well as deterioration of vision, researchers pointed out, it is not yet clear if these conditions are the result or the cause of major

drops in blood pressure. But both silent cerebrovascular damage and anterior ischemic optic neuropathy are potential risks of excessively low overnight blood pressure. Also, extra-low nighttime blood pressure dips mean an even steeper early morning blood pressure surge. Non-dippers, on the other hand, show a higher risk of target organ damage and worse cardiovascular outcomes than normal dippers, which suggests there could be a benefit to bringing down the nighttime blood pressure of non-dippers to a pattern more closely resembling normal dipping.

Many patients take their blood pressure medications at night, even though most formulations have been studied to be taken in the morning. This could be particularly concerning for patients who have “excessive dipping at night,” as their risk of excessively dropping blood pressure overnight could increase. Chronotherapeutic antihypertensives, which are designed to have their peak effect after the overnight risk period, may be an optimal therapeutic option in these patients who prefer to take their medications at night.

Scientists noted that all three groups—dippers, non-dippers, and excessive dippers—seem to get some benefit from chronotherapeutic dosing. Chronotherapeutic agents “offer further advancement towards optimizing blood pressure control, particularly in high risk patients, such those who are elderly, have renal disease, have salt-sensitive hypertension, and others,” They said.³⁰

REGULATORY IMPLICATIONS

Drugs that are reformulated as chronotherapeutics are regulated by the FDA. Chronotherapeutics present new challenges to regulators and scientists alike. For example, according to FDA, chronotherapeutic clinical studies need to consider additional parameters not usually required of other clinical trials.³¹ Among additional factors that must be considered, are:

- Time of day a drug is administered.
- Time-related biological factors, such as seasonal disorders
- Patients' normal routines (for example, eating times and sleep patterns).

DEVELOPING TIMED TECHNOLOGY

In a 1996, the American Medical Association found more than half of the physicians in the U.S. were not familiar with chronotherapy. While researchers have a long way to go to determine the cycles that govern other conditions, drug companies are realizing that chronotherapy has a future. Programmable pumps, which have already shown utility in diabetes treatment⁷, may also prove useful in delivering chemotherapy drugs at the appropriate time in the cancer cycle⁸⁻⁹, without any extra work for the patient. While technology is slowly being developed to help doctors; administer medicine at the best times, more knowledge about chronotherapy is needed. However Table 3 shows the various developed chronopharmaceutic systems and table 4 shows the various patents in the field of chronotherapy.³²

Conclusion

Generally about 75% of the doctors surveyed said they would like more treatment options to match a patient's circadian, or daily, rhythms. But chronotherapy has a way to go, considering that only 5% of the doctors surveyed said they were "very familiar" with the subject. Chronotherapy is not well recognized in the medical community, but awareness is increasing. The implications are broad in every area of medicine. However applications of chronotherapeutic drug delivery systems are now better understood for selected disease such as cancer, peptic ulcer, sleep disorder, hypertension etc. The outcomes of these systems would be a more effective and can provide quality drug delivery device for real time and ambulatory disease monitoring systems. Development of some more technologies for the large scale production of chronotherapeutic systems needs to be initiated.

Table 1: Circadian and Ultradian Rhythms in Human Tumors

Malignancy	Variable	Circadian rhythm	Peak different from normal tissue
Breast	Surface temperature 32P uptake Mitotic index	Yes Yes Yes	Yes Yes Not specified
Cervix	Surface temperature	Yes	Yes
Ovary	Cell cycle distribution	Yes (variable according to ploidy)	Yes
Non-Hodgkin lymphoma	Cell cycle distribution	Yes (variable according to stage)	Yes

Table 2. Classification of sleep disorders

Dyssomnias
1. Intrinsic sleep disorders
2. Extrinsic sleep disorders
3. Circadian rhythm sleep disorders
Parasomnias
1. Arosual disorder
2. Sleep – wake transition disorders
3. Parasomnias associated with REM
4. Other parasomnias
Sleep disorders associated with medical / psychiatric disorders
1. Associated with mental disorders
2. Associated with neurological disorders
3. Associated with other medical disorders

Table 3. Various developed chronopharmaceutic systems

Diltiazem HCl	Cardizem® LA	CEFORM® technology	Hypertension
Propranolol HCl	InnoPran® XL	DIFFUCAPS® technology	Hypertension
Verapamil HCl	Covera-HS®	OROS® technology	Hypertension
	InnoPran® XL	DIFFUCAPS® technology	Hypertension
	Verelan® PM	CODAS® technology	Hypertension

Famotidine	Pepcid®	Physico-chemical modification of the API	Ulcer
Simvastatin	Lipovas®	Physico-chemical modification of the API	Hyperlipidemia
Theophylline	Uniphyl®	CONTIN® technology	Asthama

Table 4. Various patents in the field of chronotherapy

Implantable electromechanically driven device	U.S. Pat. No. 4,003,379
Flexible system for timed controlled or position controlled drug delivery system	U.S. Pat. No. 7048945
Three Dimensional Printing® (3DP) technology	U.S. Pat. No. 5,490,962
Self-powered medication systems	U.S. Pat. No. 3,692,027
Implantable infusion device	U.S. Pat. No. 4,003,379
Pulsatile delivery	U.S. Pat. No. 6635277
Pulsatile technology	U.S. Pat. No. 5914134
Self-powered medication systems	U.S. Pat. No. 4,146,029
Pulsatile technology	U.S. Pat. No. 6217904
Microchip drug delivery devices	U.S. Pat. No. 5,797,898
Beads	U.S. Pat. No. 5439689

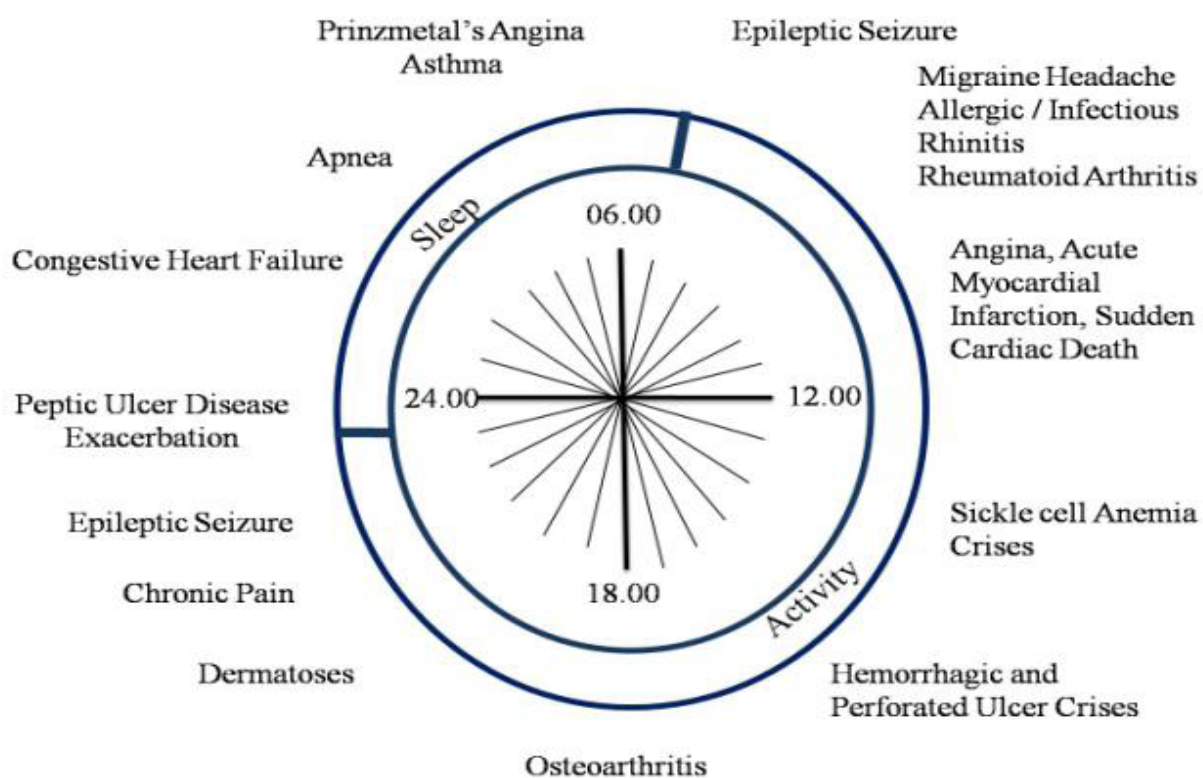


Fig.1. The circadian pattern of diseases

References

1. Pittendrigh CS. Circadian rhythms and the circadian organization of living systems. *Biological Clocks*. New York, Cold Spring Harbor Press. 1960; 25: 159–184.
2. Nelson RJ. *An Introduction to Behavioural Endocrinology*. Sinauer Associates, Inc., Massachusetts. 2005; 24: 587–589.
3. Cutolo M, Masi AT. Circadian rhythms and arthritis. *Rheum Dis Clin North Am*. 2005; 31: 115–129.
4. Born J, Lange T, Hansen K, Molle M, Fehm HL. Effects of sleep and circadian rhythms on human circulating immune cells. *J Immunol*. 1997; 158: 4454–4464.
5. Schulz P. Biological clocks and the practice of psychiatry. *Dialogues Clin Neurosci*. 2007; 9: 237-255.
6. Moore JG, Halberg F. Circadian rhythm of gastric acid secretion in active duodenal ulcer: chronobiological statistical characteristics and comparison of acid secretory and plasma gastrin patterns in healthy and postvagotomy and pyloroplasty patients. *Chronobiol Int*. 1987; 4: 101–110.
7. Rajendra Awasthi, Pravin Kumar, Vivek Kumar Pawar. Chronotherapy: Science and technology of drug scheduling on the basis of biological rhythm. *JChrDD* 2010;1(1):9-18.
8. Levi F., Chronopharmacology of Anticancer Agents, in: Redfern P.H., Lemmer B. *Physiology and Pharmacology of Biological Rhythms*, Springer, Berlin, Heidelberg, New York, 1997, Vol. 125 pp 299-332
9. Bechtold DA, Gibbs JE, Loudon AS. Circadian dysfunction in disease. *Trends Pharmacol Sci*. 2010; 31: 191-198.
10. Filipski E, King VM, Li X, Granda TG, Mormont MC. Host circadian clock as a control point in tumor progression. *J. Natl. Cancer Inst*. 2002;94:690–97.

11. Innominato PF, Focan C, Gorlia T, Moreau T, Garufi C. Circadian rhythm in rest and activity: a biological correlate of quality of life and a predictor of survival in patients with metastatic colorectal cancer. *Cancer Res.* 2009;69:4700–7.
12. Schulz P, Steimer T. Neurobiology of circadian systems. *CNS Drugs.* 2009; 23: 3-13.
13. Tampellini M, Filipinski E, Liu XH, Lemaigre G, Li XM. Docetaxel chronopharmacology in mice. *Cancer Res.* 1998;58:3896–904.
14. Turek FW. Biological clocks, circadian rhythms, and psychiatric disorders. In: *Circadian rhythms and depression. Current understanding and new therapeutic perspectives.* Edited by Julien Mendlewicz. Wolters Kluwer, 2008.
15. Mormont MC, Levi F. Cancer chronotherapy: principles, applications, and perspectives. *Cancer* 2003;97:155–69.
16. Granda TG, Levi F. Tumor-based rhythms of anticancer efficacy in experimental models. *Chronobiol. Int.* 2003;19:21–41.
17. Iurisci I, Filipinski E, Reinhardt J, Bach S, Gianella-Borradori A. Improved tumor control through circadian clock induction by Seliciclib, a cyclin-dependent kinase inhibitor. *Cancer Res.* 2006;66:10720–28.
18. Smolensky M.H., D'Alonzo G.E. Progress in the Chronotherapy of Nocturnal Asthma, in: Redfern P.H., Lemmer B. *Physiology and Pharmacology of Biological Rhythms*, Springer, Berlin, Heidelberg, New York, 1997, Vol. 125 pp 205-250.
19. Bateman JR, Clark SW. Sudden death in asthma. *Thorax.* 1979; 34: 40–44.
20. Bruguerolle B. Chronopharmacology, in: Touitou Y., Haus E., *Biologic Rhythms in Clinical and Laboratory Medicine*, Springer-Verlag, Berlin, Heidelberg, New York, pp 1994:114-137
21. Olsen NJ, Brooks RH, Furst D. Variability of immunologic and clinical features in patients with rheumatoid arthritis studied over 24 hrs. *J Rheumatol.* 1993; 20: 940–943.
22. Stone AA, Broderick JE, Porter LS, Kaell AT. The experience of rheumatoid arthritis pain and fatigue: examining momentary reports and correlates over one week. *Arthritis Care Res.* 1997; 10: 185–193.
23. Cutolo M, Masi AT. Circadian rhythms and arthritis. *Rheum Dis Clin North Am.* 2005; 31: 115–129.
24. Kirkham BW, Panayi GS. Diurnal periodicity of cortisol secretion, immune reactivity and disease activity in rheumatoid arthritis: implications for steroid treatment. *Br J Rheumatol.* 1989; 28: 154–157.
25. Cutolo M, Serio B, Cravioito, Pizzorni C, Sulli A. Circadian rhythms in rheumatoid arthritis. *Ann Rheum Dis.* 2003; 62: 593–596.
26. Nelson RJ. *An Introduction to Behavioural Endocrinology.* Sinauer Associates, Inc., Massachusetts. 2005; 24: 587–589.
27. Smolensky, M.D, Portaluppi, F. Chronopharmacology and chronotherapy of cardiovascular medications: Relevance to prevention and treatment of coronary heart disease. *Am Heart Journal.* 1999; 137: 814 – 824.
28. Peppas N, William L. Stimuli-sensitive hydrogels: ideal carriers for chronobiology and chronotherapy. *J. Biomater. Sci. Polymer Edn.* 2004; 15 (2): 125 - 144.
29. Ohta T. Circadian rhythm sleep disorders: A brief with sleep reference to long-term follow-up. *Nagoya J. Med. Sci.* 1995; 58: 83 - 93.
30. Cooke HM, Lynch A. Biorhythms and chronotherapy in cardiovascular disease. *American Journal of Hospital Pharmacy.* 1994; 51(20): 2569 - 2580.
31. Smolensky MH, Peppas NA. Chronobiology, drug delivery, and chronotherapeutics. *Adv. Drug Deliv. Rev.* 2007;59:828–51.
32. Shigehiro OHDO. Chronopharmaceutics: Pharmaceuticals Focused on Biological Rhythm. *Biol. Pharm. Bull.* 2010; 33(2): 159 - 167.