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A Review on Drug Delivery System Based on Chronotherapeutics

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Abstract:

Chronobiology is the current advancing field with the modern medicament delivery strategies have been increased and lead to the formation of the new concept chronopharmacology and Chronopharmaceutics which is nothing but the capability to deliver the active pharmaceutical agent with effective treating strength to the patient. The rhythms which are produced in the central brain have multitude life processes that include sleep as well as wake up. The genes that have the strength to restrict the activities of the rhythms are known as clock genes, which control the behavior and physiology of the humans. The application of the circadian rhythms to pharmacotherapy in at correct time through pharmaceutics is mainly through tablets or capsules. The present article mainly focuses on overview on the ongoing research on the time dependent dosage formulations for the effective treatment of various diseases.

Keywords: Chronotherapeutics, rhythms, chronopharmaceutics

1. INTRODUCTION:

Now a days the pharmaceutical industry is drastically focusing on the controlled and targeted drug delivery systems which focuses on the sustain release of the medicament or releasing the bio active agent at the target site. But there are some diseases which do not require such release pattern, which leads to focus on the therapeutic system programmed with time, such systems are able to release the drug after the preset lag phase by maintaining the beneficial drug levels throughout the day. These release systems are mainly explained by the concept of Chronotherapeutics which is the combination of chronobiology, chronopharmacology, chronopharmacokinetics, chronotherapy and Chronotherapeutics [1].

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Chronotherapeutics:

The word Chronopharmaceutics is the combination of thewords namely chronobiology and pharmaceutics. Knowing the theory of mechanism of rhythms of our body is called chronobiology. Our body contains three types of automatic rhythms.

a) Circadian rhythms: This means the oscillations that are finished in our body within 24 hours. They are self endogenous.

b) Ultrdian rhythms: This means the oscillations that are completed before 24 hrs.

Eg: sleep cycle

c) Infradian rhythms: This means the oscillations finished after 24 hrs. Eg: Menstruation.

Definition:

The method of treatment which involves the in vivo availability of the drug which is coordinated with the rhythms of the disease to overcome the side effects and increase the therapeutic efficiency [2]. The diseases which are affected by the circadian rhythms of the body are nocturnal asthma, angina, cancer, arthritis, allergic rhinitis, and hypertension. There are three components of circadian clock in humanslike input pathways, the central pacemaker and the output pathways. The information pathways hand-off tactile data to the focal pacemaker concerning outside cyclic prompts (for example light and nourishing occasions).

.**Diseases that requires the time based delivery system.**

There is a requirement of complete understanding the pathophysiology of the disease prior to the development of time based drug delivery system. If the circadian rhythms of the body playa key role on the diseasethere the pharmacokinetic and pharmacodynamics profile of the drugs is not stable in 24hrs. One of the best examples for such disease is asthma in which the changes of the circadian rhythms can be seen in the normal lung function that goes least in the early morning hours. Other disease that subject to circadian rhythms are cardiovascular disease in which there is a probability of various complications of heart like heart attack, volume of stroke, cardiac output and blood flow, hypertension [3].

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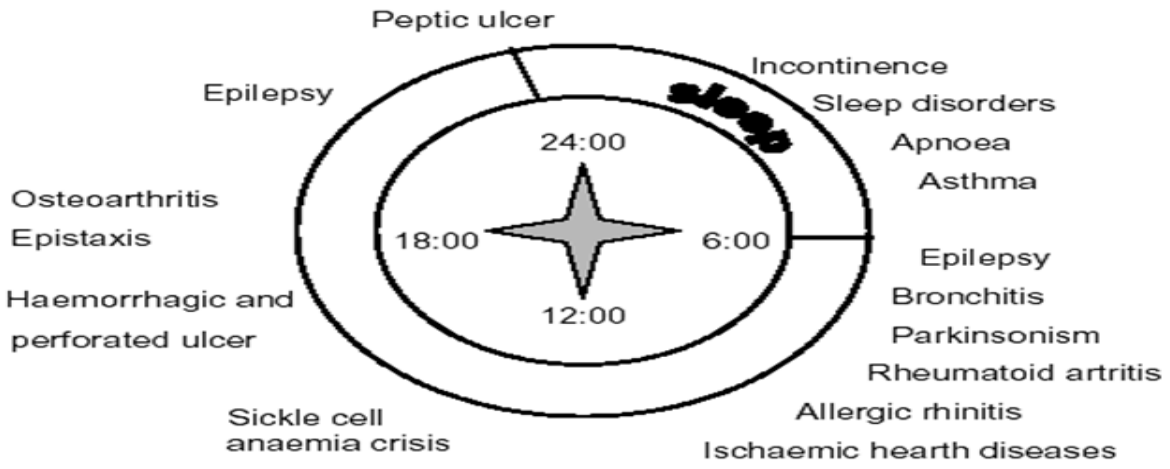

Figure 1: Diseases affected by circadian rhythm.

Circadian rhythm generation [4]:

The circadian rhythms are generated in the brain from suprachiasmatic nucleus generates the rhythm by acting on biological clock of the body and also by controlling the clock genes and also calibrates by alteration of brightness and darkness through melatonin synthesis from penal gland. Light is the most important stimulator than the other external stimuli. But the light that is used for the visual perception is completely different from the light that is used for the purpose of circadian impulse generation. Therefore this is the main reason that the humans who are blind still retain the circadian rhythms eventhough they does not have any perception of light **[5]**.There is well known information that the bodily functions of many disease states are depended on the circadian rhythms. The brain mainly releases many hormones in the morning and the remaining are released during the night time**[6]**.The pulsatile drug delivery systems are seen in pH, acid secretion, gastric emptying, and biosynthesis of cholesterol, gastro intestinal blood transfusion. The significance of the biological rhythms has been demonstrated within the research of chronopharmacological field. So there is a need to build up the formulations to meet up the therapeutic requirements which is concerning to fastidious pathological circumstances.

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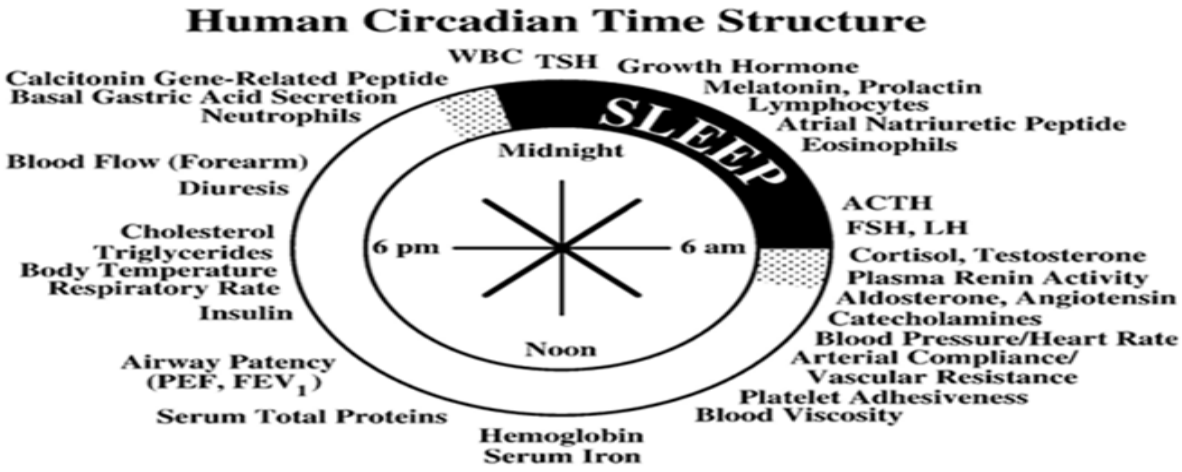

Figure2: Different hormonal functions in the structure of circadian structure.

The desired medical outcomes cannot be achieved if the strength of the drug is remained constant. The drug release varies with respect to time if the disease symptoms display circadian variation **[7]**.

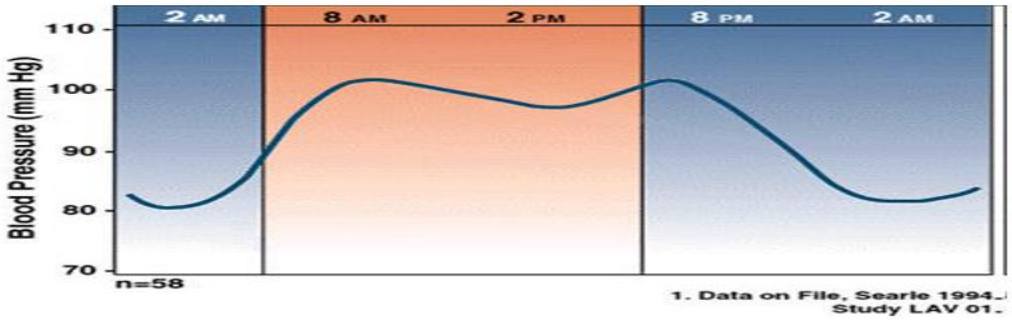

Figure3: Drug release profile in systemic circulation

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Table 1. List of technologies approved by the US-FDA

Indication/rationale for chronotherapy	Chronopharma-ceutical technology	Proprietary Name; Dosage Form	API	Date of FDA approval
Asthma/increased bronchoconstriction in morning	CONTIN	Uniphyl®; extended release tablets	Theophylline	Sept 01, 1982
Ulcer/increased gastric acid secretion in evening	Physico-chemical modification of API	Pepcid® tablets	Famotidine	Oct 15, 1986
Hypercholesterolemia/increased cholesterol synthesis overnight	Physico-chemical modification of API	Zocor® tablets	Simvastatin	Dec 23, 1991
Hypertension increased BP in early morning	OROS	Covera HS; extended release tablets	Verapamil HCl	Feb 26, 1996
Hypertension	CODAS	Verelan® PM; extended release capsules	Verapamil HCl	Nov 25, 1998
Anti-psychotic	OROS	Concerta® tablet	Methylphenidate HCl	Aug 1, 2000
Hypertension	CEFORM	Cardizem LA; Extended release tablets	Diltiazem HCl Verapamil HCl	Feb 06, 2003
Hypertension	DIFFUCAPS	Innopran XL; extended release capsules	Propranolol HCl Verapamil HCl	Mar 12, 2003
Schizophrenia	OROS	Invega	Paliperidone	Dec 19, 2006

Time based controlled release dosage forms:

There are many advantages for time based controlled release dosage forms over immediate release dosage forms. Less frequent dosage administration is possible, lower peak plasma concentrations can be achieved to avoid adverse effects and also increase the patient compliance these controlled release formulations are advantageous. Time based control release formulations are classified as rate-control release, pulsed-release, delayed release formulations, out of which delayed release formulations consists of site specific and controlled release dosage forms. Time controlled and pulsed release formulations are

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preferable when there is a need to avoid the constant drug plasma levels, especially in the treatment of early morning symptoms.

Timed release formulations:

These formulations release the drug from the dosage form after the preset time that begins before drug release. Now a days, these formulations have been extensively investigated for numerous uses. Because of the unique time release properties of time based release formulations would take the advantage of the circadian rhythms in pathophysiological functions **[8].**When there is a development of the signs according to the circadian rhythms the drug release and increase in plasma drug concentrationwould be allowed by the time based release formulations. These systems are investigated along with the release rate controlled systems for the treatment of the diseases like nocturnal asthma, rheumatoid arthritis, and various heart diseases. Medicines for such treatment should be administered to maintain the drug in therapeutic level only when it is required, so to attain this the release profile of the drug be supposed to be restrictedby means of the time rather than by rate so, in this regard there are a variety of release systems available like time clock system and sigmoidal release system **[9, 10]**.

Credit of modern chronopharmaceutical delivery systems from conventional sustained release approach.

Following reasons can be credited by moving from the conventional sustained release to chronopharmaceutical delivery.

a) First pass metabolism

A constant or sustained oral delivery of drugs is required for reduced oral bioavailability for the drugs which undergo first pass metabolism. For the drugs which undergo presystemic metabolism there is a need of fast administration of drug to reduce the presystemic metabolism**[11]**.

b) Biological tolerance

There is a decrease in the therapeutic effect of the drug due to continuous release plasma drug profiles.

c) Special chronopharmacological needs

In some physiological functions there is a well establishment of the circadian rhythms. The onset of the symptoms of many diseases will be occurred at specific

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time period of 24 hr a day. Mostly angina pectoris and nocturnal asthma is attacked in morning hours.

d) Local therapeutic need

Disorders like inflammatory bowel disease there is a need of delivery of the drugs to the specific target with no loss of the drug due to absorption in the small intestine to increase the therapeutic effect and to reduce the side effects.

e) Gastric irritation and instability in gastric fluid

The drugs with gastric irritation and chemical instability in the gastric fluid can be exacerbate by formulating as sustained release formulation.

f) Differences in absorption of drug in various gastrointestinal segments

The change in absorption characteristics of the drug in GIT is important for many drugs**[12]**.

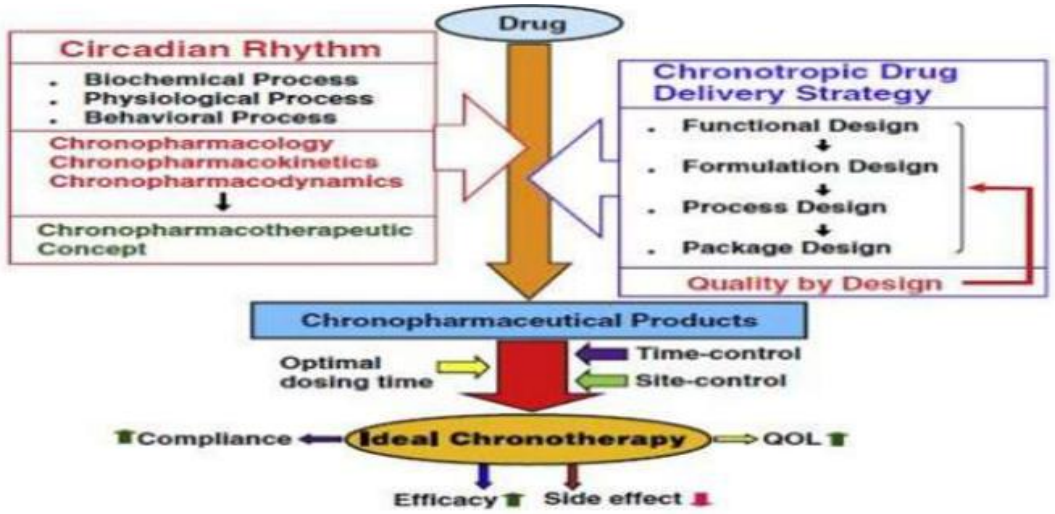

Figure 4: Development of new chronopharmaceutical drug delivery systems based on circadian rhythms.

Diseases recently targeted by pulsatile drug delivery:

Nocturnal Asthma

The attack of nocturnal asthma is mainly in the morning hour'si.e., between 2am and 6 am daily **[13].**Anti asthmatic drugs are prepared to expel the drug at the time of disease attack.Circadian variations are seen in normal lung function, which in the early morning hours

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hits a low point. Night-time asthma worsening, commonly called nocturnal asthma (NA). In this scenario, it would be preferable to have a drug delivery device administered at bedtime while releasing drugs during morning hours.

Peptic ulcer disease:

The pain of peptic ulcer disease are more severe at night due to increased acid secretion, drug administration is more active at bedtime. Not only does nocturnal administration more effectively reduce acid secretion, it also facilitates ulcer healing and decreases the recurrence of ulcer. Bedtime blocking of the H2 receptor is one of those regimes**[14]**.

Neoplastics:

Cytotoxic effects of antineoplastic drugs on healthy and diseased tissues. as predicted, in both, healthy and tumor cell biological rhythms can affect the susceptibility to these agents of healthy and cancer cells. It has been shown that drug "rhythms of susceptibility" can differ between healthy tissue and cancerous tissue. Therefore, the "correct" pacing of drug treatmentis required for ensuring effective therapeutics **[15]**.

Arthritis:

It is documented that patients with osteoarthritis have less pain in the morning hours than at night, whereas patients with rheumatoid arthritis experience more pain in the morning hours at 7. In this situation it is an obvious solution to take medication at night. NSAIDs, such as ibuprofen, must be administered 4 to 6 hours before their full value is reached**[16]**.

Myocardial Infarction:

It has been shown that the initiation of myocardial infarction is more common in the morning with 34 percent occurring by 6 A.M. and afternoon. Acute cardiac arrest and intermittent myocardial ischemia indicate an elevated morning rate. The causes of these results are suggested to be catecholamine release, platelet aggregation cortisol increase, and vascular tone increase, further ACE blockers are more active when they are given in night**[17]**.

Hypertension:

In the early morning hours (morning surge), heart rate and blood pressure are increased. Blood pressure drops from mid-afternoon and at midnight it is low. There is a rather pronounced increase in blood pressure on waking in most hypertensive patients called the morning. The systolic blood pressure increases by about 3 mm Hg / hour for the first 4-6 hours after the awakening, while the level of rate decreases**[18]**.

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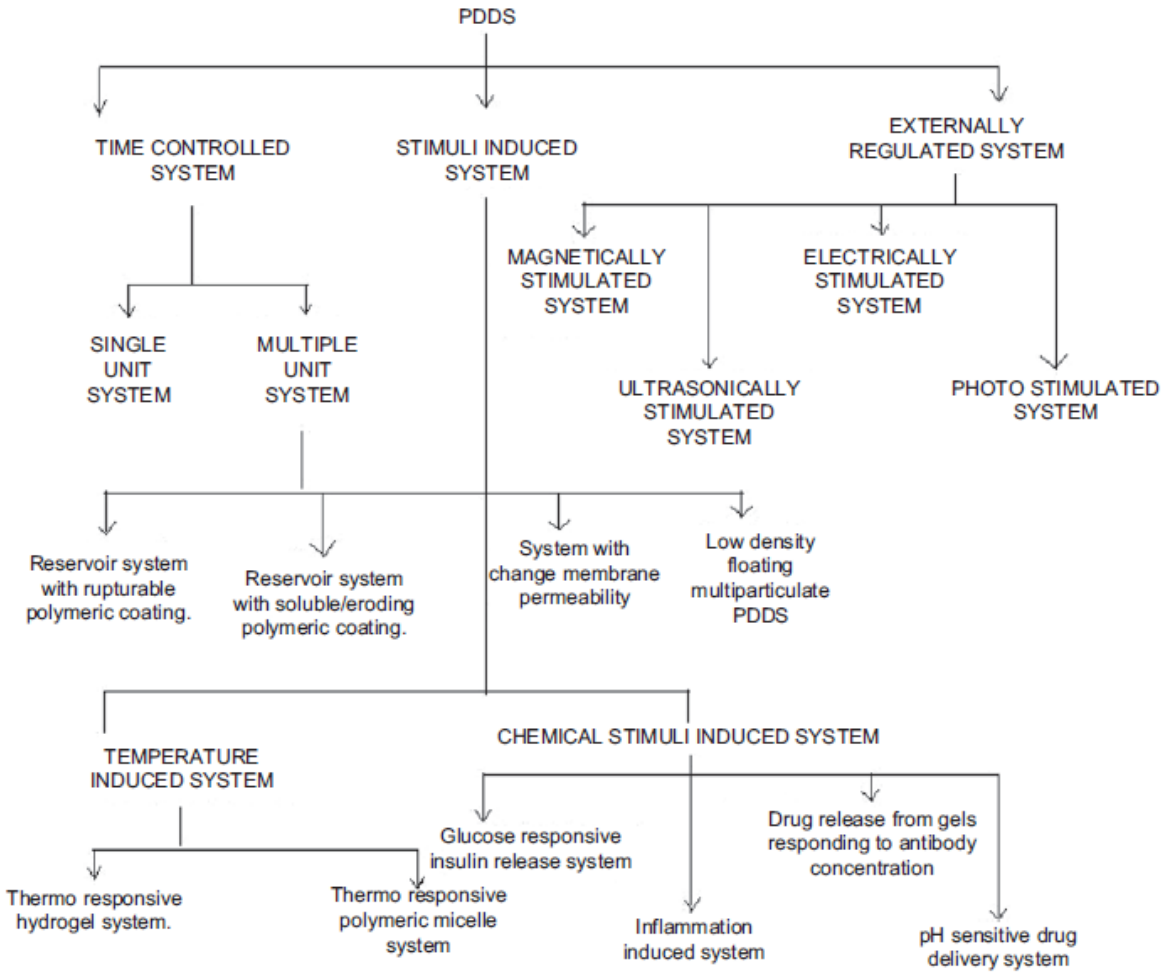

Figure 5:Types of pulsatile drug delivery systems.

Recent available formulations of chronopharmaceutical drug delivery system

There are many formulations that are developed based on the Chronopharmaceutics. They are OROS, CONTIN, CODAS, CEFORM, DIFFUCAPS AND TIMERx. The formulations are made to achieve the desired release programs by using the hydrophilic matrixes without considering the specific machines of industry**[19]**.

CONTIN technology:

There is formation of complex between the polymer and non polar solid aliphatic alcohol which act as a matrix**[20]**.

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CODAS technology:

It is elaborated as chronotherapeutic oral drug absorption system. These systems is mainly prepared for delivering the drug at bedtime and also delay the delivery for 5 hours; it is mainly due to the non enteric release scheming polymer applied to drug loaded beads**[21]**.

CEFORM technology:

This technology is mainly based on the melt spinning and produces uniform size and shape microspheres of different pharmaceutically active drug**[22]**.

OROS technology:

This technology is mainly based on the osmosis. It mainly delivers the drug to gastrointestinal tract in a time and site specific manner**[23]**.

DIFFUCAPS technology:

This technology mainly uses the capsules for the delivering of the drugs mainly unit dosage forms are delivered according to the circadian rhythms. This technology is mostly used in the treatment of hypertension**[24]**.

EGALT:

This system mainly contains resistant shell with two lag plugs in which one plug mainly contains the active drug in the center of the unit**[25]**.

GEOCLOCK:

In this system the active core is coated with two or more bases. The drug release is mainly due to erosion of the coating layer. It is based on the geometric technology**[26]**.

TIMERx:

The release of the drug from the system is mainly controlled by the rate of water penetration from the gastrointestinal tract. This is a hydrogel-based system**[27]**.

Hurdles of Chronotherapeutics drug delivery systems:

The major hurdles of the chronotherapeutic drug delivery systems are rhythmic design of the system, biomaterials, regulatory guidelines that are related to the modified dosage forms**[28]**.

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Conclusion:

In current trends the treatment of the disease based on the time is gaining interest because in the mentioned drug delivery the drug will be released when there is a need arises.Circadian rhythms are merely expressing in various types of diseases, so many more attempts have to be done for the effective delivery of the drugs to the site and it is also necessary to decrease the side effects associated with the conventional therapies. The drugs that are delivered based on the Chronopharmaceutics will provide the delivery of the medicament to the right place at right time in appropriate amount.The resistance developed by various conventional dosage and sustained release forms can be decreased by this drug delivery system. So, pulsatile drug delivery system will provide the betterment in the future for the quality of life.

REFERENCE:

[1] Abdul Sayeed, Md. M. Hamed, Mohd. Rafiq and Nahid Ali,"Pulsatile Drug Delivery Systems": Recent Technology, *IJPSR, 2013; Vol. 4(3): 960-969.*

[2] Nagar M, Singhai S, Chopra VS, Gautam N, Trivedi P. "Chronotropic systems; an emerging trend in drug delivery for pulsed release in chronopharmacotherapy". International Journal of Pharmaceutical and Clinical Research 2010; 2(1): 10-19.

[3] Sankar VR, Reddy YD, Rao AN, Dhachinamoorthy D, Chandrasekhar KB. "Chronotherapeutics: an art of dosage form designing". Journal of Pharmacy Research 2010; 3(7):690-1696.

[4] Nayana D.Patil, M.M.Bari, S.D.Barhate, "A Review on Novel Approach Pulsatile Drug Delivery System", Int. J. Pharm. Sci. Rev. Res., 21(1), Jul – Aug 2013; n° 36, 209-222.

[5] Czeisler CA, Shanahan TL, Klerman EB. "Suppression of melatonin secretion in some blind patients by exposure to bright light". N Eng J Med 1995; 332: 6-11.

[6] "Goodman & Gilman's the pharmacological basis of therapeutics 11th ed". Mcgraw-Hill medical publishing division, New York: 2006.

[7] Sajan J, Cinu Ta, Chacko Aj, Litty J Jaseeda T. "Chronotherapeutics and chronotherapeutic drug delivery systems". Trop J Pharm Res. 2009; 8(5): 467-75.

[8] White WB, Black HR, Weber MA, Elliott WJ, Bryzinski B, Fakouhi TD. "Comparison of effects of controlled onset extended release verapamil at bedtime and nifedipine gastrointestinal

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Vol-22-NO-30 Special Issue-December-2019

therapeutic system on arising on early morning blood pressure, heart rate, and the heart rate-blood pressure product". Am J Cardiol. 1998; 81: 424-31.

[9] Pozzi F, Furlani P, Gazzaniga A, Davis SS, Wilding IR. "The time clock system: a new oral dosage form for fast and complete release of drug after a predetermined lag time". Int. J. Pharm. 1994; 31: 99-108.

[10] Narisawa S, Nagata M, Danyoshi C, Yoshino H, Murata K, Hirakawa Y, Noda K. "An organic acid-induced sigmoidal release system for oral controlled-release preparations". Pharm. Res. 1994; 11(1): 111-16.

[11] Sajan J, Cinu, TA, Chacko AJ, Litty J, Jaseeda T, "Chronotherapeutics and Chronotherapeutic Drug Delivery Systems", Tropical Journal of Pharmaceutical Research, 8 (5), 2009, 467-475.

[12] Reddy R, Jyothsna M, Mod S, Chetty C, "Review on Pulsatile drug delivery system", Journal of Pharmaceutical Science and Research, 1(4), 2009, 109-115.

[13] Dethlefsen U, Repges R, Ein neues "Therapieprinzip bei nachtlichen Asthma". Med. Kli., 80, 1985, 44-47.

[14] Khan Z, Pillay V, Choonara Y E, du Toit L C , "Drug delivery technologies for Chronotherpeutics applications", Pharm. Dev.Technol., 14, 2009, 602–612.

[15] Moore G , Halberg F, "Circadian rhythm of gastric acid secretion in men with active duodenal ulcer", Dig. Dis. Sci., 31, 1986,1185–1191.

[16] Mandal A, Biswas N, Karim K, Chatterjee S, "Drug delivery system based on chronobiology- A review", Journal of Controlled Release, 147, 2010, 314-325.

[17] Prasanth V, Mitesh P, Modi, Sam T, "Pulsatile: a tool for circardian rhythm - A review", Journal of Drug delivery and Therapeutics, 2(1), 2012, 58-65.

[18] Rompicharla.B, Suria P, "A comprehensive review of pulsatile drug delivery system", International Journal of Pharmacy Research, 3(3), 2012, 106-108.

[19] Indian Pharmacopoeia, Ministry of Health and Family Welfare, Government of India. Vol.

2. Delhi: Controller of publications; 1996: A144-45.

ISSN: 0971-1260
Vol-22-NO-30 Special Issue-December-2019

[20] Kulkarni PA, Jaiswal M, Jawale SB, Shirolkar SV, Kasture PV. Development and evaluation of press coated tablets for chronopharmaceutical drug delivery using gellable and permeable polymers.Der Pharmacia Lettre2010; 2(4): 482-97.

[21] Zajc N, Obreza A, Beleb M, Srcic S.Physical properties and dissolution behaviour of nifedipine/mannitol solid dispersions prepared by hot melt method.International Journal of Pharmaceutics 2005;291:51–58.

[22] Mutalik S, Naha A, Usha AN, Ranjith AK, Musmade P, Manoj K, Anju P, Prasanna S. Preparation, *in vitro*, preclinical and clinical evaluation of once daily sustained release tablet of aceclofenac. Arch Pharm Res 2007; 30 (2): 222-34.

[23] Lieberman HA, Lachman L and Schwartz JB. Pharmaceutical dosage forms: Tablets, Vol 2; New York, Marcel Dekker; 1990: 201- 43.

[24] Percel P, Vishnupad K, Venkatesh GM. "Timedpulsatile drug delivery systems". US Patent 6, 627, 223.

[25] Verma R, Sanjay G. "Current status of drug deliverytechnologies and future directions". *Pharm Technol*,**2001**; 25: 1-14.

[26] Panoz D, Geoghegan E. Elan Corporation, UnitedStates, **1989**; 49.

[27] Staniforth JN, Baichwal AR, TIMERx®: "Novelpolysaccharide composites for controlled/programmedrelease of drugs in the gastrointestinal tract". *ExpertOpin Drug Deliv*, **2005**; 2: 587-595.

[28] Neeraj Singh, Nisha, Vivek Gill, Parina Gill, Sukhbir Singh, "Chronopharmaceutical Drug Delivery System-A Guided Therapy" Int. Res J Pharm. App Sci., 2013; 3(4):84-87.