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## Important Aspects and Fundamentals of Chronotherapeutic Drug Delivery System for Optimizing Therapeutic Effect. A Review

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### ABSTRACT

Chronotherapeutic drug delivery system is useful in the treatment of disease, in which drug availability is timed to match rhythm of disease, in order to optimize therapeutic effect and minimize side effects. There is an impact of circadian rhythms in the symptoms of certain diseases like asthma, arthritis, depression, ulcer, allergic rhinitis, sleep disorders etc. The human body follows the solar/ lunar adaptations known as biological clock. The role of circadian rhythms in the mechanisms of disease and the pharmacokinetics and pharmacodynamics of medications constitutes a challenge to drug-discovery and drug-delivery scientists. We must strive to develop intelligent drug-delivery systems that can affect a target cell or organ system at that circadian time when it is possible to optimize desired therapeutic outcomes and minimize or avert adverse effects. The present article covers findings about the effects of biorhythms on various disorders, and their implications for drug therapy are discussed. Here we also reviewed the design of novel chronopharmaceutical drug delivery systems that might be able to release the therapeutic agents at predetermined intervals.

**Keywords:** Chronotherapy, Circadian rhythm, Chronopharmaceutics, Chronopharmacokinetics.

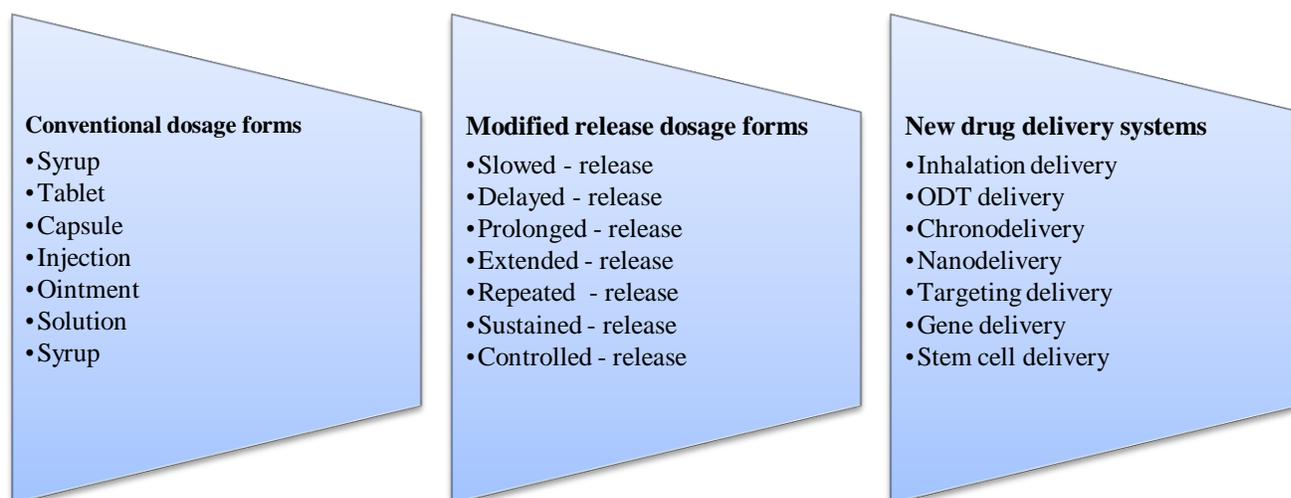
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## INTRODUCTION:

In order to increase the effectiveness of drug there are many approaches which have been applied. The pharmaceutical formulations are direct ingestion for oral administration and orally administered drugs are generally absorbed from the gastrointestinal tract<sup>1-7</sup>. Here one of the techniques is described which is chronotherapeutic drug delivery system. Many functions of the human body show considerable change in a day. These variations cause changes both in disease state and in plasma drug concentrations<sup>8, 9,10, and 11</sup>. To maintain the effective plasma drug concentration, frequent administration is required. Due to poor drug efficacy, the incidence of side effects, the frequency of administration and patient compliance of the conventional drug preparations. Some Conventional, modified and new drug delivery system are shown in Figure 1<sup>12-15</sup>. The human circadian rhythm is based on sleep activity cycle, is influenced by our genetic makeup and hence, affects the body's functions day and night (24-hour period)<sup>15,16</sup>. Coordination of biological rhythms with medical treatment is called *Chronotherapy*. Chronotherapy considers a person's biological rhythms in determining the timing and amount of medication to optimize a drug's desired effects and minimize the undesired ones. Study of influence of biological rhythm on the effects of medication is known as chronopharmacology while the science of study of biological rhythms is known as chronobiology. To understanding the biological time keeping the idea came that these rhythms must affect how the body responds to drugs administered over the course of the day<sup>17,18,19</sup>. The Chronotherapy of a medication may be accomplished by the appropriate timing of conventionally formulated tablets and capsules, and a special drug delivery system to synchronize drug concentrations to rhythms in disease activity<sup>20,21</sup>.



**Figure1: Progress of Pharmaceutical Preparations**

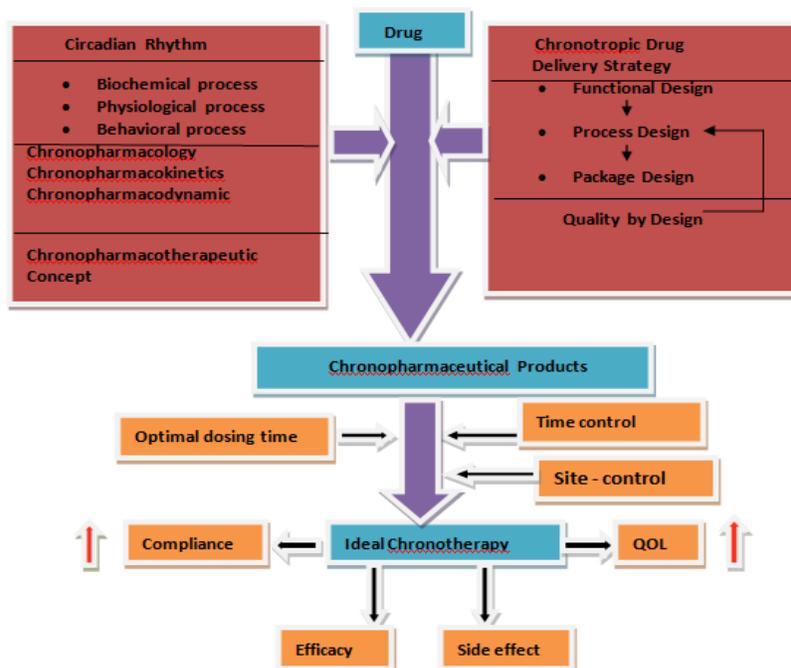
Chronotherapy is relevant when the risk or intensity of the symptoms of disease vary with time as in the case of allergic rhinitis, arthritis, asthma, myocardial infarction, congestive heart failure, stroke and peptic ulcer disease<sup>22,23,24,25</sup>. Traditionally, drug delivery systems have focused on constant/sustained drug output with the objective of minimizing peaks and valleys of drug concentrations in the body to optimize drug efficacy and to reduce adverse effects as compared to immediate release preparations<sup>26,27,28</sup>.

### **Chronotherapeutic**

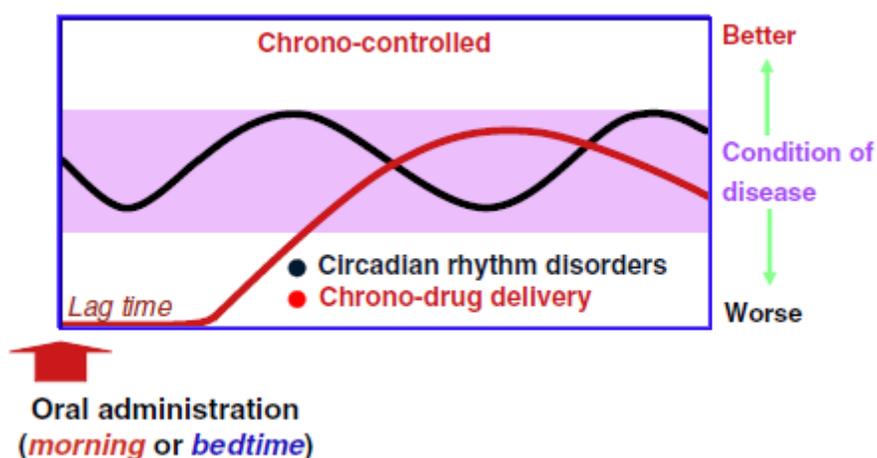
The term "chrono" basically refers to the observation that every metabolic event undergoes rhythmic changes in time. Perhaps the best known and studied chronobiology frequency is the circadian rhythm which approximates the earth's 24-hour rotation around the sun<sup>29</sup>. Researchers have recently concluded that both disease states and drug therapy are affected by a multitude of rhythmic changes that occur within the human body<sup>30</sup>. Chronotherapeutic refers to a treatment method in which in vivo drug availability is timed to match rhythms of disease in order to optimize therapeutic outcomes and minimize side effects. It is based on the observation that there is an interdependent relationship between the peak-through rhythmic activity in disease symptoms and risk factors, pharmacologic sensitivity and pharmacokinetics of many drugs<sup>31</sup>. The new chronotropic DDS technology for delivering drugs precisely in a time-controlled fashion in accordance with circadian rhythms may be developed as a chronopharmaceutical product to treat different human diseases, as proposed by Figure 2. Rationale behind designing these chronotropic DDSs is to release the drug at desired time based on pathophysiological need of disease, which results in the improvement of therapeutic efficacy<sup>32</sup> and patient-compliance. Chronotherapeutic is the new discipline of medical treatment of drugs by considering patient's biological rhythms in determining the timing of medication to optimize a drug's desired effects and minimize side effects. Chronotherapeutic goal is to provide optimal therapy by administering medication in the right amount, to the desired target organ, at the most appropriate time<sup>33,34</sup>. The drug delivery for disease treatment is coordinated with circadian rhythms as proposed in Figure 3.

### **Circadian Time Structure**

Circadian rhythms are the rhythm in the chronotherapeutic and the dysfunction of circadian rhythms can affect the brain functioning and it can be improved by the chronotherapeutic approach. Circadian rhythms are self-sustaining, endogenous oscillations that occur with a periodicity of about 24 hours. Circadian rhythm regulates several body functions such as metabolism, physiology, behavior, sleep patterns, hormone production, and so on. The circadian



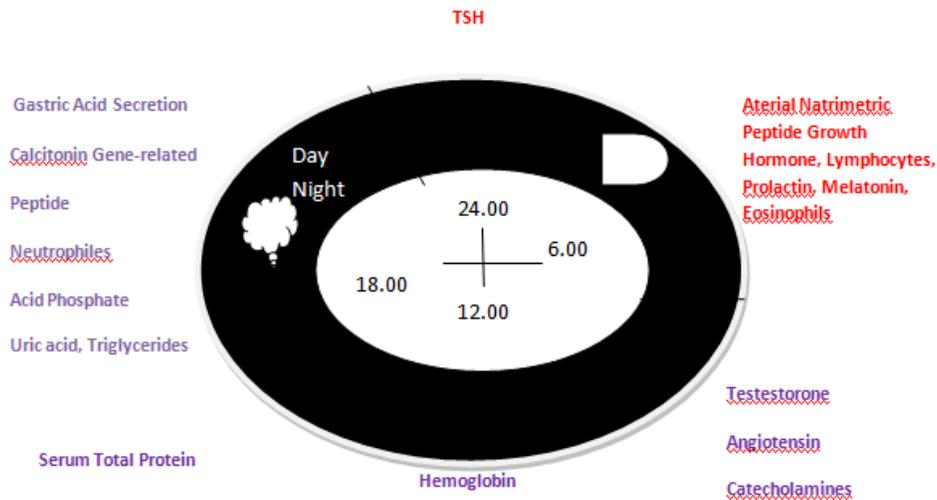
**Figure 2: Design and development of new chronotropic DDSs in accordance with cardiac rhythm of human body**



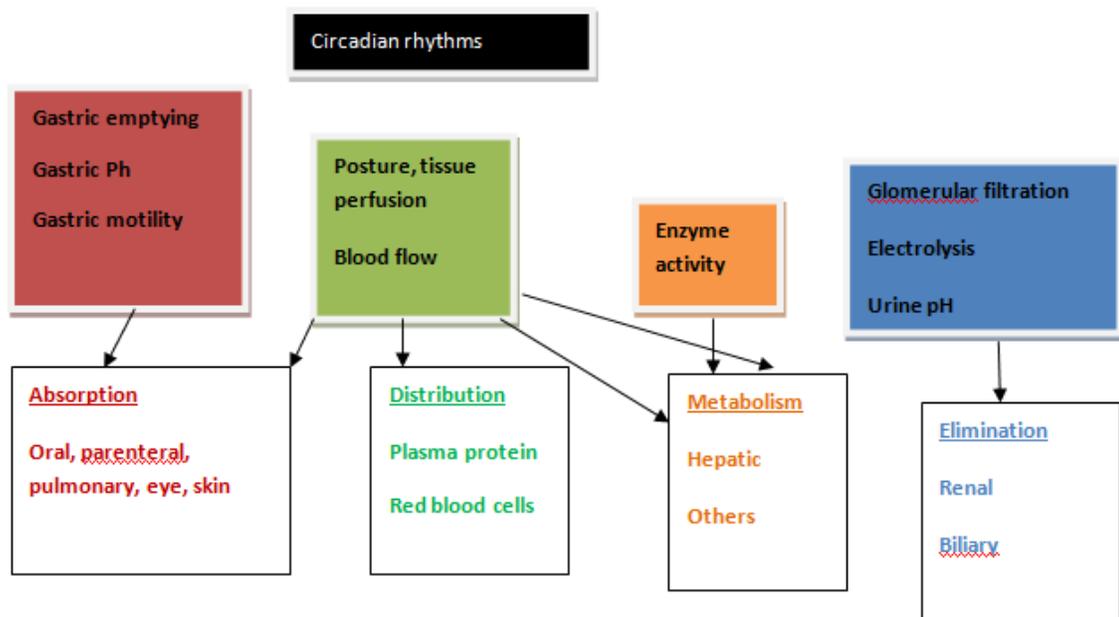
**Figure 3: An ideal chronotherapeutic drug delivery according to the cardiac rhythm disorders of the patient**

rhythm not only affects most physiological functions but also influences the absorption, distribution, metabolism, and elimination (ADME) of drugs, leading to changes in drug availability and target cell responsiveness<sup>35-39</sup>. Circadian rhythms can change the sleep-wake cycles, hormone release, body temperature, and other important bodily functions driving the alteration of various physiological, biochemical, and behavioral processes Figure 4<sup>40,41</sup>. Thus, the time-dependent dynamic bioprocesses in human body are significantly dependent on circadian variations, and so constant delivery of a drug into the human body seems both unnecessary and

undesirable. Timing the administration of some medications in accordance with the body's circadian rhythm may significantly affect the drug's pharmacokinetics and pharmacodynamics Figure 5<sup>42</sup>.



**Figure 4: Human circadian time structure – dependent pulsatile hormones secretion.**

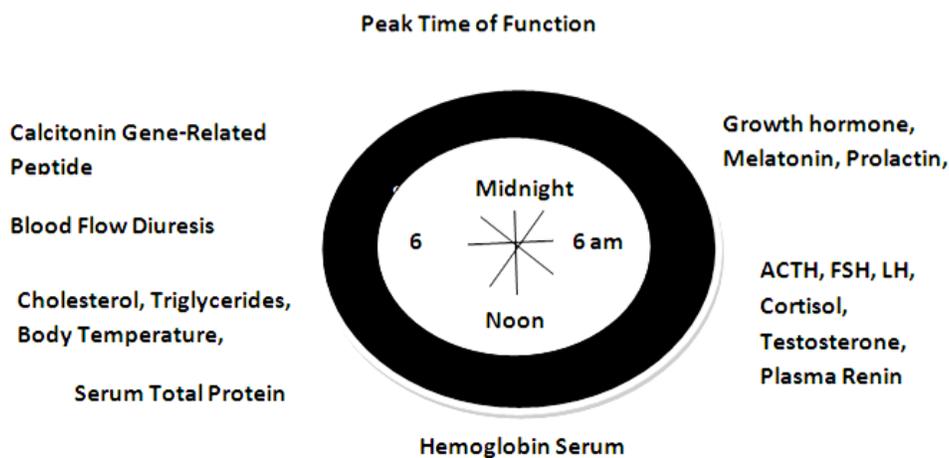


**Figure 5: Effect of circadian rhythm on the ADME of drugs**

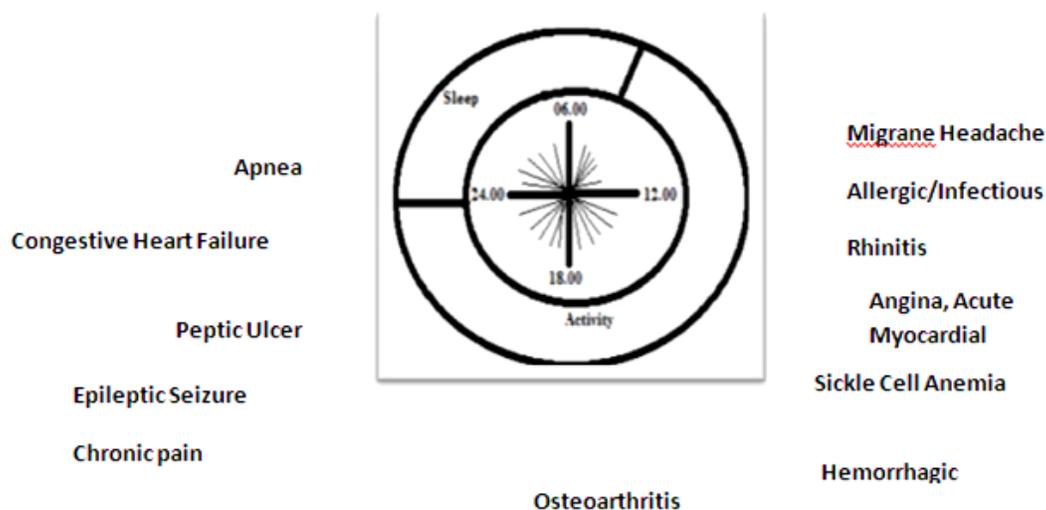
### Circadian Rhythms of Diseases

The biological rhythm studies help in defining the temporal organization of human beings. One means of illustrating the human circadian time structure is to depict the peak time of 24-h rhythms on a clock--like diagram. The 24 h clock pattern of diseases showing prominent day-night patterns when symptoms of disease are most frequent is shown in Figure 6. Variation in the severity of many diseases over a 24-hour

period is well known diseases such as bronchial asthma, myocardial infarction, angina pectoris, rheumatic disease, ulcers<sup>43</sup>, diabetes, and attentiondeficit syndrome, hypercholesterolemia and hypertension show symptomatic changes due to circadian rhythm city<sup>44-46</sup>. Aggravation of asthmatic attacks occur after midnight or in the early morning due to limited lung function promoted by circadian changes at that time. Many common diseases also display a marked circadian variation during onset or exacerbation of symptoms, as shown in Figure 7.



**Figure 6: Human circadian time structure. Shown is the approximate peak time of circadian (24-h) rhythms of selected biological variables in persons adhering to a normal routine of daytime**



**Figure 7: The circadian pattern of diseases**

Asthma may be the most common disease with the largest circadian variation. Because asthma has such a striking circadian variation, several types of chronotherapy have been tried. In one study, use of a timed-release formulation of theophylline (Theo-24) achieved therapeutic drug

concentrations during the night and avoided toxic levels during the day. Asthma is well suited for chronotherapy, with beta 2- agonists and oral corticosteroids<sup>47, 48, 49</sup>. Symptoms of asthma occur 50 to 100 times more often at night than during the day. Many circadian dependent factors appear to contribute to the worsening of nocturnal asthmatic symptoms<sup>50, 51</sup>.

### **Cancer**

An important issue in the treatment of cancer is its tolerability by patients. Drugs having good therapeutic effect by killing tumor cells are always limited in their use by their toxicity on healthy tissues. Experimental studies in cancer chronotherapy were initially performed by Halberg et al and Hrushesky et al, conducted research on chronotherapy for gynecological and genitourinary cancers including advanced renal cell carcinoma. These studies demonstrated the superiority of chronotherapy with respect to response and side effects when compared to conventional chemotherapy<sup>52, 53, 54</sup>. Chemotherapy may be more effective and less toxic if cancer drugs are administered at carefully selected times that take advantage of tumor cell cycles while less toxic to normal tissue<sup>55</sup>.

### **Arthritis**

The new cyclooxygenase-2 inhibitors effectively relieve osteoarthritis symptoms when taken in the morning; better results are obtained in rheumatoid arthritis when part of the dose is taken in the evening. The cardinal signs of rheumatoid arthritis are stiffness, fever<sup>56, 57</sup> swelling and pain of joints of the body characteristically most severe in the morning. Ankylosing spondylitis is characterized by swelling and discomfort of the joints of the back. Taking long-acting non steroidal anti-inflammatory<sup>58, 59, 60</sup> like flurbiprofen, ibuprofen<sup>58</sup> and ketoprofen and indomethacin once-a-day forms optimizes their therapeutic effect and minimizes their side effects<sup>60, 61, 62</sup>.

### **Hypertension**

Many antihypertensive drugs do not control the early morning blood pressure, when given once daily early in the morning<sup>63, 64</sup>. Hermida et al studied the impact of antihypertensive treatment and the time of therapy on the circadian pattern of blood pressure in hypertensive patients with diabetes mellitus. Blood pressure was measured at 20 min intervals from 07:00 to 23:00 h and at 30 min intervals at night for 48 consecutive h. Blood pressure was reduced during diurnally active h, but not during nocturnal sleep, as compared to untreated patients ( $P < 0.001$ ). Results from this study indicate the need to establish a proper chronotherapeutic scheme that could reduce BP and modify the altered circadian profile into a BP pattern, associated to a lower cardiovascular risk<sup>65, 66, 67</sup>.

## Diabetes:

In type I diabetes the circadian rhythms of insulin and its action are of physiological interest and clinical importance<sup>68</sup>. 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<sup>69, 70, 71</sup>.

## DEVELOPMENT OF CHRONOTHERAPEUTIC DELIVERY SYSTEMS

The chronopharmaceutical technologies based on physical and/or chemical activation for controlled drug release that is intended for different route of administration have been described in detailed<sup>72</sup>. Examples of technologies that may be used for parenteral routes in chronotherapy include Chronomodulating infusion pumps (i.e. Melodie™, Panomat™ V5, Synchroned™, Rhythmic™) and controlled release microchip strategies<sup>73</sup>. A basic chronotherapeutic system consists of a drug containing core and a barrier layer of polymer to control drug release from the core. Microchips can be used to control release of drug from the systems to obtain controlled release program. The advantages of PDDS extend to drugs with chronopharmacological behaviors, where night time dosing is required and for various diseases that is influenced by circadian rhythms<sup>74, 75</sup>. Since PDDS has a unique mechanism of delivery, whereby a drug releases rapidly after a lag time, various PDDSs have appeared on the markets that replace modified-release dosage forms. Various release patterns are illustrated in Figure 8<sup>76-83</sup>.

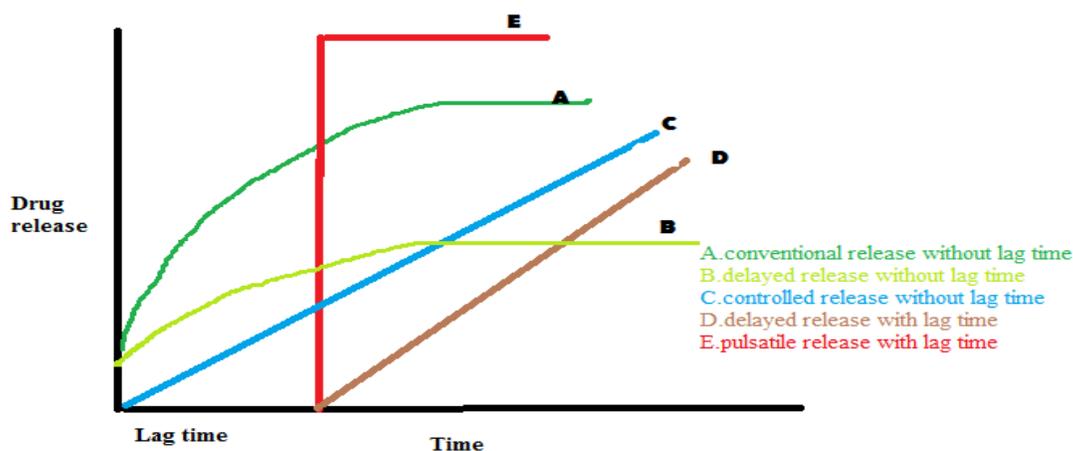


Figure 8: Different release patterns for various pharmaceutical dosage forms

**Chronopharmacokinetics** Chronopharmacokinetics is defined as the predictable rhythmical changes dependant on the absorption, distribution, metabolism, and elimination are influenced by different physiological functions that may vary with the dosing. Chronopharmacodynamic phenomenon and demonstrate that time of drug administration influences the kinetics of drug. Thus, the time of administration of a drug is an important source of variation which must be taken into account in kinetic studies and particular methodological aspects of chronokinetic are needed<sup>84,85</sup>. The main aim of chronokinetic studies is to control the time of administration which among others, can be responsible for variations of drug kinetics but also may explain chronopharmacological effects observed with certain drugs.

**Table 1. List of the chronopharmaceutical dosage forms marketed and the pulsatile drug delivery technologies used.**

<b>Drug</b>	<b>Chronopharmaceutical technology</b>	<b>Drug release mechanism</b>	<b>Timing of drug administration</b>	<b>Indication for chronotherapy</b>	<b>Ref.</b>
Rabeprazole sodium	Enteric coating technology	Delayed – release	After morning meal	Healing of duodenal ulcers	87
DiltiazimHCl	CEFORM microsphere technology	Diffusion/erosion	Bedtime	Hypertension	88
Carvedilol phosphate	Micropump platform	Immediate-release/controlled – release	Morning with food	Heart Failure, heartattack, Hypertension	89
Molsidomine	Geomatrix technology	Swelling, gelling, Erosion	Morning	Chronic angina pectoris	90, 91
Verapamil HCl	OROS technology	Osmotic regulation	Bedtime	Hypertension	92, 93
Dexlansoprazole	DDR technology	Dual drug release	Fasting state before breakfast	Healing of erosive esophagitis	94, 95
Gliclizide	Hydrophilic matrix technology	Swelling, diffusion, erosion	Breakfast time	Type II diabetes	96, 97
Glipizide	OROS technology	Osmotic regulation	Morning with food	Type II diabetes	98, 99

### CHRONOPHARMACEUTICS

Chronopharmaceuticshas been described as a branch of pharmaceutics devoted to the design and evaluation of drug delivery system that release a bioactive agent at a rhythm that ideally matches the biological requirement of a given disease therapy. Youan<sup>19</sup> one of the goals of these systems is to provide zero order, constant rate, delivery of bioactive agents, however it is now well known that living organisms do not require constant rate delivery or provide “zero order”

response to drugs<sup>86</sup>. Pharmaceutical companies have focused on developing and commercializing chronopharmaceutical drug products that fulfill unmet medical needs in the treatment of various diseases. In this review, examples of currently marketed chronopharmaceutical dosage forms, the manufacturing techniques applied, drug release mechanisms, and the timing of drug administration are collected and compiled in Table 1.

## CONCLUSION

In this review article advances in Chronotherapy has been demonstrated the importance of biological rhythms in treatment of disease and this has led to a new approach to the development of novel drug delivery system as a Chronotherapeutic Drug Delivery System. Chronotherapeutic goal is to provide optimal therapy by administering medication in the right amount, to the desired target organ, at the most appropriate time. The effectiveness and toxicity of many drugs depending on dosing time required 24 h rhythms of biochemical, physiological and behavioral processes under the control of circadian clock. The application of biological rhythm to chronotherapy may be correlated by the appropriate timing of dosing of drug delivery systems to synchronize drug concentrations to rhythms in disease state. It also determined the use of chronotherapeutic may play a role in determining an optimal treatment in other diseases, such as rheumatoid arthritis, asthma, hypertension, myocardial infarction and peptic ulcer. The outcomes of these systems would be a more effective and can provide quality drug delivery device for real time and ambulatory disease system.

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