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# Pulsatile Drug Delivery System: A Review

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**Abstract:** The pulsatile drug delivery system has carried off a lot of importance in drug delivery technology in the last 30 years the aim of the present work was to formulate and evaluate an oral pulsatile drug delivery system to achieve time release of melonixcam, based on chronopharmaceutical approach for the treatment of anti-inflammatory agent. Thus drug can be delivered at righttime, in right amount and at right site of action by use of such approach. A pulse must be planned sothat a complete and rapid medication release is accomplished after the lag time. Holds good promises and provides benefit to the patients suffering from chronic problems like arthritis, asthma, hypertension etc.

**Keywords:** melonixcam, pulsatile drug delivery system, HPMC K4M, pulsatile delivery, circadian rhythm, pulsincapTM

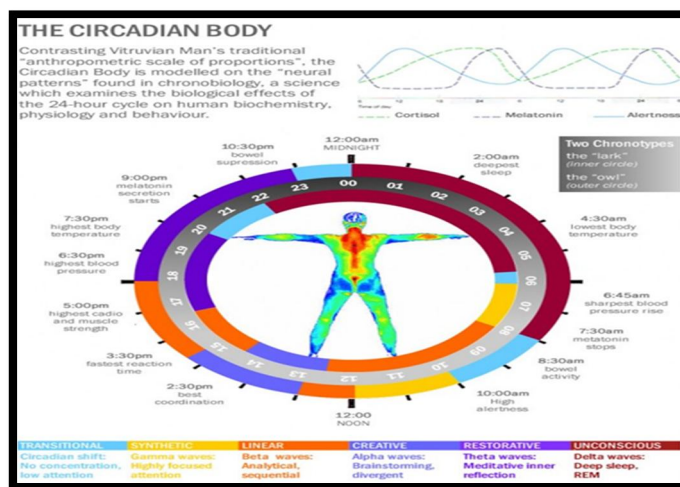
## I. INTRODUCTION

### A. Pulsatile Drug Delivery System

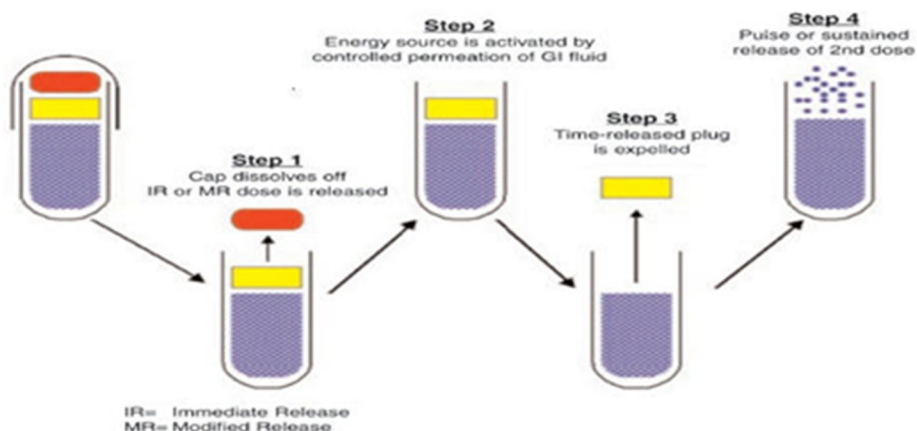
With the advancement of technology in the pharmaceutical field, drug delivery systems have drawn an increasing interest over the last few decades. Nowadays, the emphasis of pharmaceutical formulation research has turned towards the development of more efficacious drug delivery systems with already existing molecules rather going for new drug discovery because of the inherent hurdles posed in drug discovery and development process.

- 1) **First pass Metabolism:** Some drugs, such as beta blockers and salicylamide, undergo extensive first pass metabolism and require rapid drug input to saturate metabolizing enzymes in order to minimize presystemic metabolism. Thus, a constant /sustained oral method of delivery would result in reduced oral bioavailability
- 2) **Biological Tolerance:** Continuous release drug plasma profiles are often accompanied by a decline in the pharmacotherapeutic effect of the drug, e.g., biological tolerance of transdermal nitroglycerin.
- 3) **Special Chronopharmacological Needs:** Circadian rhythms in certain physiological functions are well established. It has been recognized that many symptoms and onset of disease occur during specific time periods of the 24 hr day, e. g., asthma and angina pectoris attacks are most frequent in the morning hours.
- 4) **Local Therapeutic Need:** For treatment of local disorders such as inflammatory bowel disease, delivery of compounds to the site of inflammation with no loss due to absorption in small intestine is highly desirable to achieve the therapeutic effect and to minimize side effects.

Drugs which exhibit tolerance should not be delivered at a constant rate, since the drug effect decreases with time at constant drug level. In addition, drug toxicity increases with time when drug levels are held constant. In such cases it is preferable to opt for dosage form which will provide desired concentration of drug at particular time point only.



- a) *Circadian*: This term is derived from the Latin words "circa" which means around, and "dies" which means day. Circadian rhythms are self-sustaining, endogenous oscillations that occur with a periodicity of about 24 Hours and regulate many body functions like-metabolism, sleep pattern, hormone production etc. Several physiological processes in humans vary in a rhythmic manner, in synchrony with the internal biological clock [12].
  - b) *Ultradian*: oscillation is a kind of oscillation with a shorter duration (more than one cycle per 24 h) E.g. 90 minutes sleep cycle.
  - c) *Infradian*: Oscillations that last for more than 24 hours are considered to be periodic (less than one cycle per day). E.g. Monthly Menstruation
  - d) *Seasonal*: Seasonal affective disorder (SAD), which causes depression in susceptible people during the short days of winter.
- Necessity Of Pulsatile Drug Delivery Systems** There are many conditions and diseases where sustained release formulations don't show good efficiency. In such cases Pulsatile Drug Delivery System is applicable.



### B. Advantages

- 1) It Improve bioavailability.
- 2) It has less adverse effects.
- 3) It reduces dose size.
- 4) It reduces dosage frequency.
- 5) Improves patient compliance.
- 6) It protects mucosa from irritating drugs.
- 7) It extends day time, night time activity.
- 8) It has a specific drug target.

## II. CLASSIFICATION OF PULSATILE DRUG DELIVERY SYSTEM VARIOUS APPROACHES OF PULSATILE DRUG

Pulsatile drug delivery system can be broadly classified into three classes;

- 1) Time controlled pulsatile drug delivery
- 2) Stimuli induced pulsatile drug delivery
- 3) Externally regulated pulsatile drug delivery

### A. Time Controlled Pulsatile Drug Delivery

#### 1) Single unit Pulsatile Systems

- a) Capsule based systems E.g. Pulisincap system
- b) Capsular system based on Osmosis
  - 'PORT' System
  - System based on expandable orifice
  - Delivery by series of stops
  - Pulsatile delivery by solubility modulation

- c) Pulsatile system with Erodible or soluble barrier coatings.
    - The chronotropic system
    - 'TIME CLOCK' System.
    - Compressed tablets
    - Multilayered Tablets
  - d) Pulsatile system with rupturable coating
- 2) *Multiparticulate / Multiple unit systems: s*
- a) Pulsatile system with rupturable coating E.g. Time –controlled Explosion system (TCES)
  - b) Osmotic based rupturable coating system E.g. Permeability controlled system
  - c) Pulsatile delivery by change in membrane permeability E.g. Sigmoidal release system.

### III. CAPSULAR SYSTEM BASED ON OSMOSIS

#### A. 'PORT' System

The Port system was developed by Therapeutic system research laboratory Ann Arbor, Michigan, USA, and consists of a capsule coated with a semipermeable membrane. Inside the capsule was an insoluble comprising of osmotically active agent and the drug formulation. When this capsule interacted with the dissolution fluid, the semipermeable membrane allowed the entry of water, which caused the pressure to develop and the insoluble particles.

#### B. System Based on Expandable Orifice

To deliver the drug in liquid form, an osmotically driven capsular system was developed within which the liquid drug is absorbed into extremely porous particles, that release the drug through an orifice of a semipermeable capsule upheld by an expanding osmotic layer once the barrier layer is dissolved.

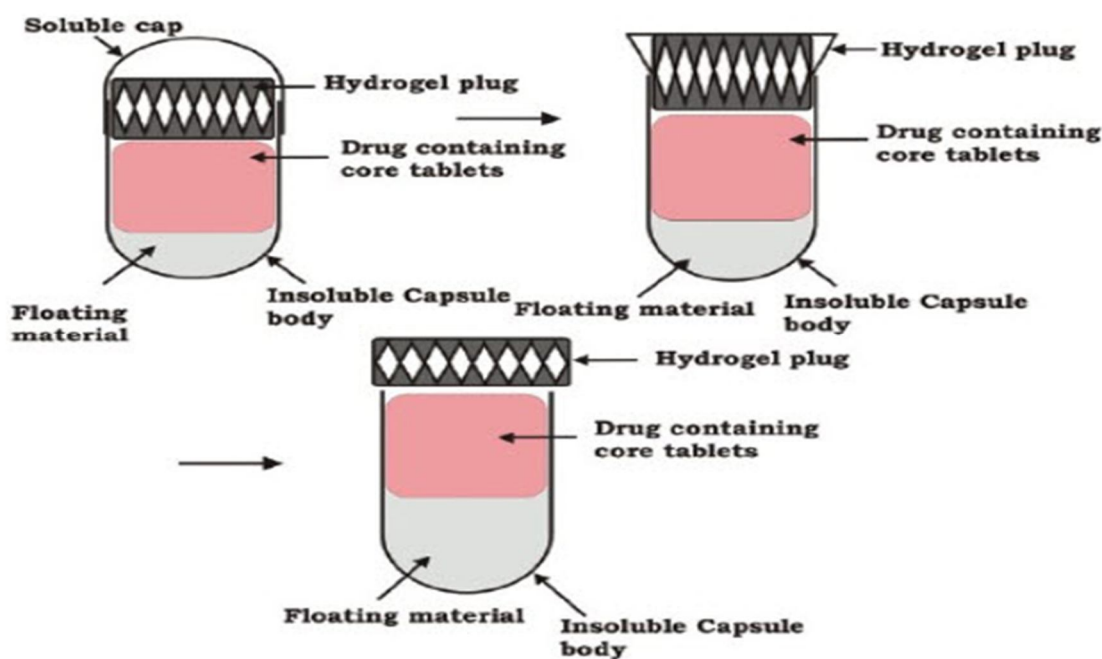


Fig.4: Drug release mechanism from PORT system

#### C. Pulsatile System with Erodible or soluble Barrier Coatings

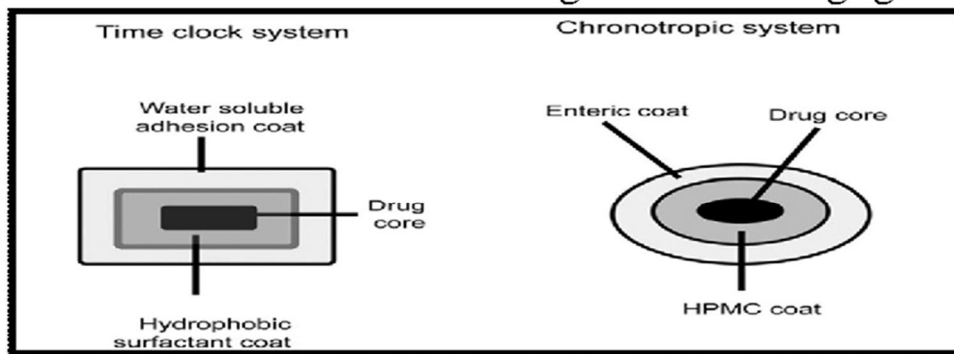
Most of the pulsatile drug delivery systems are reservoir devices coated with a barrier layer. This barrier erodes or dissolves after a specific lag period, and the drug is subsequently released quickly from reservoir The core. The lag time depends on the thickness of the coating layer.

**D. Chronotropic System**

The Chronotropic® system consists of a drug-containing core coated by hydrophilic swellable hydroxypropylmethyl cellulose (HPMC), that is responsible for a lag phase in the onset of release.[25- 27] Additionally, through the application of an outer gastricresistant enteric film, the variability in gastric emptying formulation can also be achieved through use of swelling agent.

**IV. THE CHRONOTROPIC SYSTEM**

formulation can also be achieved through use of swelling agents.



**Figure 10: The aqueous dispersion coat is followed by a water soluble coat to improve adhesion to the core coat.**

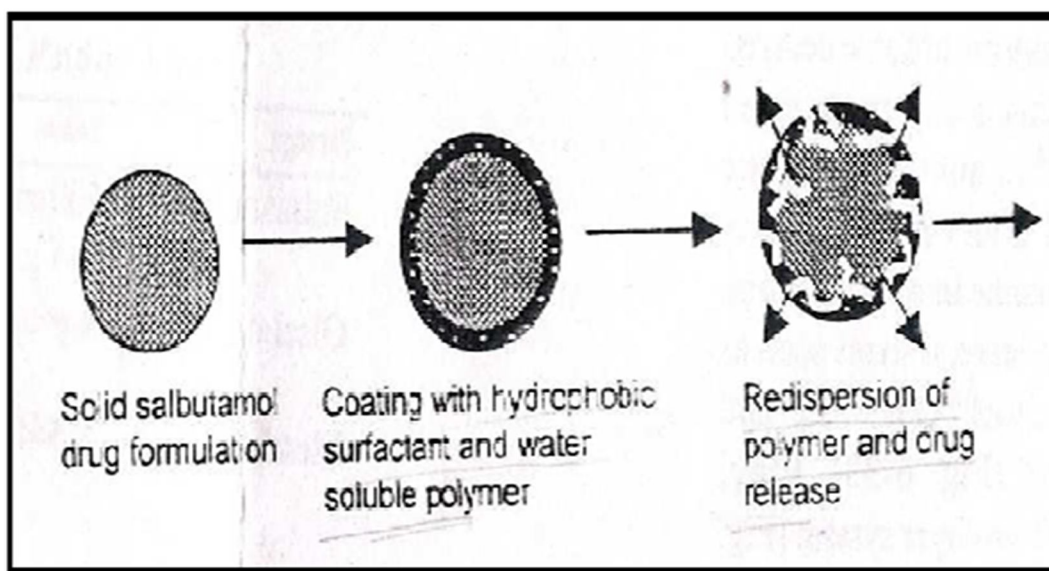
This system has shown reproducibleresults in vitro and in vivo. The effect of low calorie and high calorie meal on the lag time was studied using gamma scintigraphy. The mean lag time of drug release was 345

Additionally, through the application of an outer gastricresistant enteric film, the variability in gastric emptying time can be overcome, and a colon-specific release can be obtained, relying on the relative reproducibility of small intestinal transit time.

The lag time is controlled by the thickness and the viscosity grades of HPMC.[29] Both in-vitro andin vivo lag times correlate well with the applied amount of the hydrophilic retardin polymer. The system is suitable for both tablets and capsules.

Thickness of the film. After the lag time, i.e., the time required for rehydration, the core immediately releases the drug.

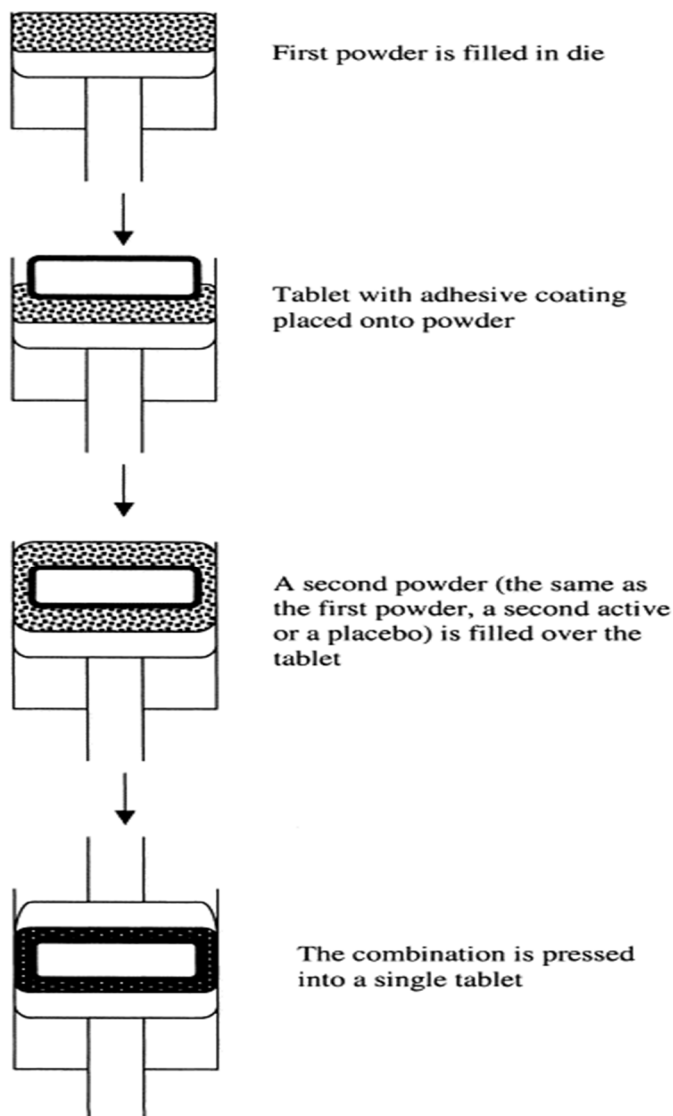
**V. TIME CLOCK SYSTEM**



### A. Compressed Tablets

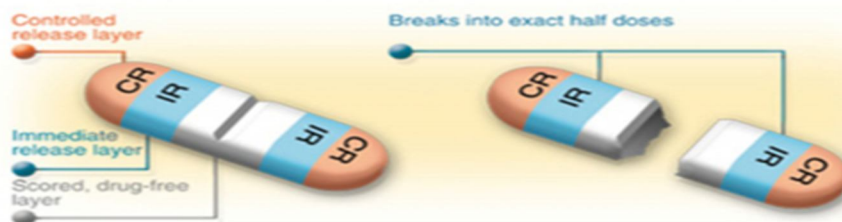
Compression coating can involve direct compression of both the core and the coat, obviating needs for separate coating process and use of coating solutions. The outer tablet of the compression-coated tablet provides the initial dose, rapidly disintegrating in the stomach and the inner layer is formulated with components that are insoluble in gastric media but are released in the intestinal environment. [21] Materials such as hydrophilic cellulose derivatives can be used. Compression is easy on laboratory scale. The major drawbacks of the technique are that relatively large amounts of coating materials are needed and it is difficult to position the cores correctly. hygroscopic, light sensitive, oxygen labile or acid-labile drugs. cheap.

- 1) Press-coated pulsatile drug delivery systems can be used to protect hygroscopic, light sensitive, oxygen labile or acid-labile drugs.
- 2) Press-coated pulsatile drug delivery systems are relatively simple and cheap.
- 3) These systems can involve direct compression of both the core and the coat.
- 4) Materials Such as hydrophobic, hydrophilic can be used in press-coated pulsatile drug delivery system.
- 5) Press-coated pulsatile drug delivery systems involve compression which is easy on laboratory scale.
- 6) Press-coated pulsatile formulations release drug after “lag-time”.
- 7) Press-coated pulsatile drug delivery formulations can be used to separate incompatible drugs from each other or to achieve sustained release.



### B. Multilayered Tablets

A delivery design with two pulses was gotten from a three-layered tablet containing two medication-containing layers separated by a medication-free gellable polymeric hindrance layer. This three-layered tablet is coated on three sides with impermeable ethyl cellulose, and the top portion was left uncoated. Upon contact with dissolution medium, the initial dose incorporated into the top layer was released rapidly from the non coated surface. The second pulse is obtained from the bottom layer after HPMC layer gets eroded and dissolved. The rate of gelling or dissolution of the barrier layer control the appearance of the second pulse. The gelling polymers reported include cellulose derivatives like HPMC, methyl cellulose, or polyvinyl alcohols of various molecular weights and the coating materials include ethyl cellulose, cellulose-acetate propionate, methacrylic polymers, acrylic and mehtacrylic co-polymers, and polyalcohols.



## VI. DISEASES AND CHRONOTHERAPEUTICS

Diseases are presently targeted for chronopharmaceutical formulations which are have enough scientific backgrounds to justify PDDS as compared to the conventional drug administration approach .they include hypercholesterolemia, asthma, cancer, duodenal ulcer, arthritis, diabetes, neurological disorders, cardiovascular diseases (e.g. Hypertension and acute myocardial infarction) and colonic delivery. The rationale for chronotherapy/pulsatile release for each of these diseases will be briefly reviewed and given as follows.

### A. Cardiovascular Diseases

Cardiovascular diseases include hypertension and angina, or chest pain, also follow a definite circadian rhythm .in cardiovascular disease capillary resistance and vascular reactivity is higher in the morning and decreases latter in the day. Platelet agreeability is increased and fibrinolytic activity is decreased in the morning, which leading to a state of relative hyper coagulability of the blood. Because of this reason the frequencies of myocardial infarction and of sudden cardiac death are more during a period from morning to noon. Ambulatory blood pressure measurements show a significant circadian variation to characterize blood pressure .this variation is affected by a variety of external factors such as ethnicity, gender, autonomic nervous system tone, vasoactive hormones, and hematological and renal variables. Increased heart rate, blood pressure, imbalanced autonomic tone, circulating level of catecholamine controlling the cardiac arrhythmias show important circadian variation and trigger the genesis of the circadian pattern of cardiac arrhythmias. Atrial arrhythmias appear to exhibit circadian pattern usually with a higher frequency in the daytime and lower frequency in the night time with the abnormal foci under the same long term autonomic regulation as normal pacemaker tissue. According to study ventricular atrophy arrhythmias shows late morning peak in the patients with myocardial infarction sometime in the distant past morning peak and afternoon peak in patients with recent myocardial infarction.

### B. Hypertension In hypertension

Heart rate and blood pressure are increased in the early morning hours (morning or a.m. Surge). The blood pressure increases from midafternoon and is minimum at midnight. In mostly high blood pressure patients, there is a rather distinct rise in blood pressure upon awakening that is called the morning or —a.m. the systolic blood pressure rises approximately 3mm hg/hour for the first 4-6 hours post-awakening, while the rate of increase of diastolic blood pressure is approximately 2mm hg/hour.

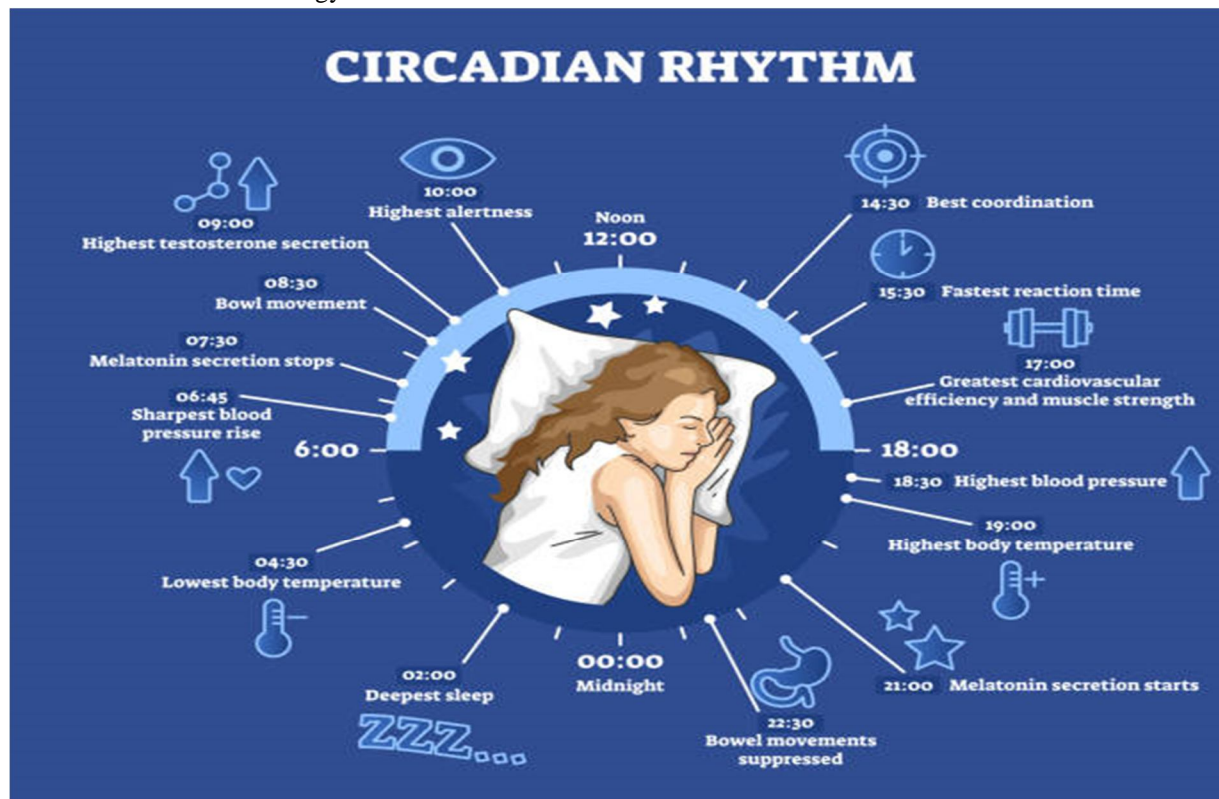
### C. Neoplastics Antineoplastic

Drugs cause cytotoxic effects on healthy and diseased tissues. As would be predicted that, the biological rhythms of both healthy and tumor cells may influence the susceptibility of normal and malignant cells to these agents. It has been confirmed that susceptibility rhythms to drugs may differ between healthy tissue and cancerous tissue. Therefore, the correct timing of drug treatment may reduce host toxicity, increase the maximum drug tolerance, and ultimately result.

#### D. Peptic Ulcer Disease

Peptic ulcer is because of maximal acid secretion the peptic ulcer disease pain and perforation of gastric and duodenal ulcers are more frequent at night, administration of drugs at bedtime is more efficient in peptic ulcer disease. Nocturnal administration not only reduces acid secretion more effectively but also promotes ulcer healing and reduces ulcer reappearance. Bedtime h<sub>2</sub>-receptor blockade is one such regimen used for peptic ulcer disease.

Biological clock time for chronobiology.



Biological clock time for chronobiology

#### E. Myocardial Infarction

Occurrence of myocardial infarction has been shown to be more frequent in the morning .in which 34% events occurring between 6 a.m. And noon. Acute cardiac arrest and transient myocardial ischemia shows an increased frequency in morning. The causes for these findings have been suggested to be release of catecholamine, Cortisol increase in the platelet aggregation and vascular tone. ACE inhibitors shows greater results when they are administered during night. Atenolol, Nifedipine and Amlodipine are more effective when administered at night.

#### F. Duodenal Ulcer

Many of the functions of the gastrointestinal tract are subject to circadian rhythms. Like gastric acid secretion is highest at night, while gastric and small bowel motility and gastric emptying are all slower at night. These biorhythms have important implications in the pharmacokinetics of orally administered drugs. At nighttime, when gastric motility and emptying are slower, drug disintegration, dissolution, and absorption may be slower. In peptic ulcer patients, gastric acid secretion is highest during the night. Suppression of nocturnal acid is an important factor in duodenal ulcer healing. Therefore, for active duodenal ulcer, once daily dosage regimen of H<sub>2</sub> antagonist at bedtime is the recommended for better implication. The theoretical problems which associated with a sustained or profound decrease of 24-h intra gastric acidity include the threat of enteric infection and infestation, potential bacterial overgrowth with possible n-nitrosamine formation, drug-induced hyper gastrinaemia and disturbed protein digestion. In night when these types of potential problems occurs. That time the management of simple peptic ulceration is necessary, it appears sensible to use and the minimum intervention required. For such a reason administration of h<sub>2</sub>-receptor blockade at bedtime is give effective.

#### G. Arthritis



The patients suffering from osteoarthritis are reported to have less pain in morning hours as compared to night, while patients suffering from rheumatoid arthritis feel more pain in the morning hours than nights. In this case taking medication at night is an apparent solution. NSAID such as Ibuprofen need to be administered 4 to 6 hours before achieving their maximum benefit, as a result peak will occur at patients waking and the effect will be decline as patient start to wake up. There is circadian rhythm in the plasma concentration of c reactive protein and interleukin – 6 of patients with rheumatoid arthritis.

#### H. Hypercholesterolemia

Hypercholesterolemia is the diverse directions of circadian changes in lipid fractions. In patients and normal subjects may contribute to alteration in the rhythm city of other metabolisms and in the blood coagulation system, thus leading to various complications a circadian rhythm occurs during hepatic cholesterol synthesis. However, this rhythm varies according to individuals. Indeed, there is a large variation in plasma mevalonate concentrations between individuals. Therefore cholesterol synthesis is generally higher during the night than during daylight, and diurnal synthesis may represent up to 30%–40% of daily cholesterol synthesis many individuals display a paradoxical synthesis, with an inverted diurnal cholesterol synthesis. It seems therefore that cholesterol is synthesized during the night as well as during daylight or however it is higher in night. However the maximal production occurs early in the morning, i.e. 12 h after the last meal. studies with 3-hydroxy-3- methylglutaryl-coenzyme (HMGCoA) inhibitors have suggested that evening dosing was more effective.

#### I. Disadvantages

- 1) Content of drug is low.
- 2) Incomplete release of drug

## VII. CONCLUSION

We conclude that the pulsatile drug delivery system play a very key role in the treatment of many chronological diseases like Asthma, Hypertension, Rheumatoid Arthritis etc. Pulsatile drug delivery system is most suitable for time specific and site specific delivery of drugs. Although sustained and controlled drug delivery systems have gained a lot of success and application in field of medication, these systems fail to deliver drug according to circadian behavior of diseases for which pulsatile systems are beneficial.

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