The study of biological rhythms and their mechanisms is known as chronobiology. They are regulated by sunlight. There are three types of mechanical rhythms in our body: 4,21

• Ultradian
• Infradian
• Circadian

Ultradian rhythms
They are the rhythms that have a period of shorter than 24 hours.

Infradian rhythms
They are the rhythms which have a frequency ranging from 28 hours to 6 days. 4

Circadian rhythms
The term “circadian”, coined by Franz Halberg, comes from the Latin circa, “around”, and diem of dies, “day”, meaning literally “approximately one day”. Our body appears to be genetically programmed to function on roughly a 24-hour cycle. These rhythms allow organisms to anticipate and prepare for precise and regular environmental changes. They are important in determining the sleeping and feeding patterns of animals, including human beings. There are clear patterns of core body temperature, brain wave activity, hormone production, and other biological activities linked to this cycle. Some people function best in the morning while others have their peak in the noon or evening. If our normal rhythm is disrupted we tend to become anxious. E.g. many people have difficulty in adjusting to swing-shift work schedules. e.g. in sleep wake cycle an animal will settle into a 24 hour cycle activity and sleep even if deprived of light. Diurnal blood pressure fluctuations are super imposed by a 24-hour rhythm with lower levels during the night and higher in the day. 4 (Figure 1)

Biological rhythms

INTRODUCTION
Oral route of drug delivery is considered the favoured and most user-friendly means of drug administration having highest degree of patient compliance, as a result of which much effort are aimed to identify orally active candidates that would provide reproducible and effective plasma concentrations in vivo. Oral drug delivery can be classified in three categories,

A. Immediate release- which is designed for immediate release of drug for rapid absorption. B. Sustained release designed on the basis of span-sule technology for extended absorption.

C. Controlled and targeted drug delivery system- which are more of pharmaceutical and clinical superiority over conventional immediate release pharmaceutical products. 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. A reduced dosing frequency and improved patient compliance can also be expected for the controlled/sustained release drug delivery systems, compared to immediate release preparations.

Chronobiology
Time is a component of a measuring system used to sequence events, to compare the duration of events and the interval between them, and to quantify the motion of objects. Every event in life depends on time. It is not possible to imagine the life we are leading without the invention of the concept of time. Time brings regulation in our life and unless we regulate ourselves we are not able to do anything. 4

Keywords: pulsatile drug delivery systems, circadian rhythms, chronotherapy
**Chronotherapeutics**

It is the purposeful delivery of medications in unequal amounts over time during 24 hours. Chronotherapeutics takes into account rhythm determinants in disease pathophysiology, chronopharmacology of medications, dose and administration time to optimise desired/ minimise adverse effects.

Chronotherapeutics does not involve only new medicines but also the improved applications of established once in a different and more biologically efficient manner. In certain instances, chronotherapeutics may be achieved by unequal morning and evening dosing schedules of sustained release 12 hours medication systems, better timing of conventional once a day medication/delivery systems, or application of special tablet and capsule formulations dosed at designated times to proportion medications over 24 hours in synchrony with rhythm determined requirements. The current first generation, drug delivery systems used in chronotherapeutics demands strict adherence by patients to recommended dosing time to achieve desired outcome.

“The goal of chronotherapeutics is the management or reversal of existing acute or chronic medical conditions” & “Delivery of drugs to the body at the right time, at optimal dose”.

<table>
<thead>
<tr>
<th>CLASS</th>
<th>DRUGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular drugs</td>
<td>Verapamil, Propranolol, Dilatazem, Nifedipine, Enalapril</td>
</tr>
<tr>
<td>Antiasthmatic drugs</td>
<td>Mehyldipronisolone, Prednisolone, Albuterol, Iborubine, Theophylline</td>
</tr>
<tr>
<td>Anticancer drugs</td>
<td>Cisplatin, Oxaliplatine, Doxorubicin, 5-fluorouracil</td>
</tr>
<tr>
<td>Non steroid anti-inflammatory drugs</td>
<td>Ibuprofen, Ketoprofen, Indomethacin, Tenoxicam,</td>
</tr>
<tr>
<td>Anti ulcer drugs</td>
<td>Cimetidine, Ranitidine, Famotidine, Pirenzipine, Omeprazole</td>
</tr>
<tr>
<td>Anticholesterol drugs</td>
<td>Simvastatin, Lovastatin</td>
</tr>
</tbody>
</table>

Oral controlled drug delivery systems release the drug with constant or variable release rates. These system shows a typical pattern of drug release in which the drug concentration is maintained in the therapeutic window for a prolonged period of time (sustained release), thereby ensuring sustained therapeutic action as shown in figure 2. But there are certain conditions which demand release of drug after a period of no drug release which is known as lag time. Diseases where constant drug levels are not preferred, but needs a pulse of therapeutic concentration in a periodic manner acts as a push for the development of “Pulsatile Drug Delivery Systems”.

Figure 2: Release pattern of Sustained Release Dosage Form (A) and Pulsatile Release Dosage Form (B).

A delivery system with a release profile that is characterized by a time period of no drug release (lag time) followed by a rapid and complete drug release (pulse release) can be called as an ideal pulsatile drug delivery system. In other words, it is required that a drug should not be released at all during the initial phase of dosage form administration. Lag time is defined as the time between when a dosage form is placed into an aqueous environment and the time at which the active ingredient begins to get released from the dosage form; precisely lag time is an interval of no drug release followed by rapid drug release.

![Figure 3: Drug release profiles (A) Pulsatile, (B) Conventional and (C) Extended release](image)

**Need for of Pulsatile Drug Delivery Systems**

There are many conditions and diseases where sustained release formulations do not show good efficacy. The shift from conventional sustained release approach to modern pulsatile delivery of drugs can be credited to the following reason(s):

1. **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 24 hour day, e.g., asthma and angina pectoris attacks are most frequent in the morning hours.

2. **First pass metabolism**
   - Some drugs, such as beta blockers, and salicylamide, undergo extensive first pass metabolism and require fast drug input to saturate metabolizing enzymes in order to minimize pre-systemic metabolism. Thus, a constant/sustained oral method of delivery would result in reduced oral bioavailability.

3. **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.

4. **Local therapeutic need**
   - For the treatment of local disorders such as inflammatory bowel disease, the delivery of compounds to the site of inflammation with no loss due to absorption in the small intestine is highly desirable to achieve the therapeutic effect and to minimize side effects.

5. **Drug absorption differences in various gastrointestinal segments**
   - In general, drug absorption is moderately slow in the stomach, rapid in the small intestine, and sharply declining in the large intestine. Compensation for changing absorption characteristics in the gastrointestinal tract may be important for some drugs. For example, it is rational for a delivery system to pump out the drug much faster when the system...
reaches the distal segment of the intestine, to avoid the entombment of the drug in the faeces.

6. Gastric irritation or drug instability in gastric fluid: For compounds with gastric irritation or chemical instability in gastric fluid, the use of a sustained release preparation may exacerbate gastric irritation and chemical instability in gastric fluid.

Table 2: Diseases requiring Pulsatile Drug Delivery

<table>
<thead>
<tr>
<th>Diseases</th>
<th>Chronological behavior</th>
<th>Drugs used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peptic ulcer</td>
<td>Acid secretion is high in the noon and at night</td>
<td>H₂ blockers</td>
</tr>
<tr>
<td>Asthma</td>
<td>Precipitation of attacks during night or at early morning hours</td>
<td>β₂ agonist, Antihistaminics</td>
</tr>
<tr>
<td>Cardiovascular diseases</td>
<td>BP is at its lowest during sleep cycle and rises in early morning</td>
<td>Nitroglycerin, Calcium channel blocker, ACE inhibitors etc</td>
</tr>
<tr>
<td>Arthritis</td>
<td>Pain in the morning &amp; more pain in the night</td>
<td>NSAIDs, Glucocorticoids</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Increase in blood sugar level after meal</td>
<td>Sulfonylurea, Insulin, Biguanide</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>Cholesterol synthesis is generally higher during night than day</td>
<td>HMG CoA reductase inhibitors</td>
</tr>
</tbody>
</table>

CLASSIFICATION OF PULSATILE DRUG DELIVERY SYSTEMS

Based on the biologic environment pulsatile drug delivery systems (PDDS) can be classified in site-specific and time-controlled systems. Drug release from site-specific systems depends on the environment in the gastrointestinal tract, e.g., on pH, presence of enzymes, and the pressure in the gastrointestinal tract. In contrast, time-controlled DDS are independent of the biological environment. The drug release is controlled only by the system. Time-controlled pulsatile delivery has been achieved mainly with drug-containing cores, which are covered with release-controlling layers 10,11,12,19,31.

Methodologies for the PDDS can be broadly classified into four classes;

I. Time controlled pulsatile release
   A. Single unit system
   B. Multi-particulate system

II. Stimuli induced
   A. Thermo-Responsive Pulsatile release
   B. Chemical stimuli induced pulsatile systems

III. External stimuli pulsatile release
   A. Electro responsive pulsatile release
   B. Magnetically induced pulsatile release

IV. Pulsatile release systems for vaccine and hormone products.

I. TIME CONTROLLED PULSATILE RELEASE SYSTEM

These time-controlled systems can be classified as single unit (e.g., tablet or capsule) or multiple unit systems.

A. Single unit systems

B. Multicarticulate systems
   A. SINGLE UNIT SYSTEM
   i. Pulsatile System Based On Capsule

Different single-unit capsular pulsatile drug delivery systems have been developed. A general architecture of such systems consists of an insoluble capsule body housing a drug and a plug. The plug is removed after a predetermined lag time owing to swelling, erosion, or dissolution. The Pulsincap® system is an example of such a system that is made up of a water-insoluble capsule body filled with drug formulation. The body is closed at the open end with a swellable hydrogel plug. Upon contact with dissolution medium or gastrointestinal fluids, the plug swells, pushing itself out of the capsule after a lag time. This is followed by a rapid drug release. Manipulating the dimension and the position of the plug can control the lag time.

Pulsincap System

For water-insoluble drugs, a rapid release can be ensured by inclusion of effervescent agents or disintegrants. The plug material consists of insoluble but permeable and swellable polymers (e.g., polymethacrylates), erodible compressed polymers (e.g., hydroxypropylmethyl cellulose, polyvinyl alcohol, polyethylene oxide), congealed melted polymers (e.g., saturated polyglycolated glyceralides, glyceryl monooleate), and enzymatically controlled erodible polymer (e.g., pectin). These formulations were well tolerated in animals and healthy Volunteers, and there were no reports of gastro-intestinal irritation. However, there was a potential problem of variable gastric residence time, which was overcome by enteric coating the system to allow its dissolution only in the higher pH region of small intestine19-20.

ii) Port System

The Port® System consists of a gelatin capsule coated with a semipermeable membrane (e.g., cellulose acetate) housing an insoluble plug (e.g., lipidic) and an osmotically active agent along with the drug formulation. When in contact with the aqueous medium, water diffuses across the semi permeable membrane, resulting in increased inner pressure that ejects the plug after a lag time. Coating thickness controls the lag time. The system showed good correlation in lag times of in-vitro and in-vivo experiments in humans. The system was proposed to deliver methylphenidate for the treatment of attention deficit hyperactivity disorder (ADHD) in school-age children. Such a system avoids a second daily dose that otherwise would have been administered by a nurse during school hours.
iii) Delivery by a series of stops:
This system is described for implantable capsules. The capsule contains a drug and a water-absorptive osmotic engine that are placed in compartments separated by a movable partition. The pulsatile delivery is achieved by a series of stops along the inner wall of the capsule. These stops obstruct the movement of the partition but are overcome in succession as the osmotic pressure rises above a threshold level. The number of stops and the longitudinal placements of the stops along the length of the capsule dictate the number and frequency of the pulses, and the configuration of the partition controls the pulse intensity. This system was used to deliver porcine Somatotropin.

iv) Delivery by solubility Modulation:
These systems contain a solubility modulator for pulsed delivery of variety of drugs. The system was especially developed for delivery of salbutamol sulphate. The compositions contain the drug (salbutamol sulphate) and a modulating agent, sodium chloride (NaCl). The amount of NaCl was such that it was less than the amount needed to maintain saturation in a fluid that enters the osmotic device. The pulsed delivery is based on drug solubility. The modulating agent can be a solid organic acid, inorganic salt, or organic salt.

v) Delivery by reservoir systems with erodable or soluble barrier coatings:
Most of the pulsatile drug delivery systems are reservoir devices coated with a barrier layer. Barrier erodes or dissolves after a specific lag period, and the drug is subsequently released rapidly. The time lag depends on the thickness of the coating layer.

The Time Clock® System:

![Figure 7: The Time Clock System](image)

It consists of a solid dosage form coated with lipid barriers containing carnauba wax and bees wax along with surfactants, such as polyoxyethylene sorbitan monooleate. This coat erodes or emulsifies in the aqueous environment in a time proportional to the thickness of the film, and the core is then available for dispersion. The major advantage of this system is its ease of manufacture without any need of special equipment. The disadvantage of this system is a premature drug release when the penetrating water dissolves the drug.

- The Chronotropic® system:

![Figure 8: The Chronotropic® system](image)

It consists of a drug-containing core coated by hydrophilic swellable hydroxypropylmethyl cellulose (HPMC), which is responsible for a lag phase in the onset of drug release. Time lag is controlled by the thickness and the viscosity grades of HPMC used in coating the drug core. The system is suitable for both tablets and capsule formulations.

B. MULTIPARTICULATE SYSTEMS:

Multi-particulate drug delivery systems are mainly oral dosage forms consisting of a multiplicity of small discrete units, in which the active substance is present as a number of small independent subunits. They provide many advantages over single-unit systems because of their small size, less inter and intra-subject variability in gastrointestinal transit time, reduced adverse effects and improved tolerability, no risk of dose dumping, flexibility in design and finally Improve stability. However, there are some draw backs in this system, which include lack of manufacturing reproducibility, high cost of production, multiple formulation steps and also the need of advanced technologies.

There are different types of multiparticulate systems and these are enumerated and explained below:

i. Pulsatile System Based on Rupturable Coating:
This is a Multiparticulate system in which drug is coated on non-pariel sugar seeds followed by a swellable layer and an insoluble top layer. The swelling agents used include superdisintegrants like sodium carboxymethyl cellulose, sodium starch glycolate, L-hydroxypropyl cellulose, etc. Upon ingress of water, the swellable layer expands, resulting in rupture of film with subsequent rapid drug release. The release is independent of environmental factors like pH and drug solubility. The lag time can be varied by varying coating thickness or adding high amounts of lipophilic plasticizer in the outermost layer.

ii. Time controlled expulsion system
This system is based on a combination of osmotic and swelling effects. The core contains the drug, a low bulk density solid and/or liquid lipid material (e.g., mineral oil) and a disintegrant. The core is further coated with cellulose acetate. Upon immersion in aqueous medium, water penetrates the core displacing the lipid material. After the depletion of lipid material, internal pressure increases until a critical stress is reached, which results in rupture of the coating material. Another system is based on a capsule or tablet composed of a large number of pellets consisting of two or more pellets or part.
iii. Sigmoidal Release System:
This consists of pellet cores comprising drug and succinic acid coated with ammonia- methacrylate copolymer USP/NF type B. The time lag is controlled by the rate of water influx through the polymer membrane. The water dissolves acid and the drug in the core. The acid solution in turn increases permeability of the hydrated polymer film. The different types of acids that can be used include succinic acid, acetic acid, glutaric acid, tartaric acid, malic acid, or citric acid.

iv. Low density floating Multiparticulate pulsatile systems:
Low density floating multiparticulate pulsatile dosage forms reside only in stomach and not affected by variability of pH, local environment or gastric emptying rate. These dosage forms are also specifically advantageous for drugs either absorbed from the stomach or requiring local delivery in stomach.33

II. STIMULI INDUCED PULSATILE RELEASE SYSTEM
The mechanisms of drug release include ejection of the drug from the gel as the fluid phase synergestes out, drug diffusion along a concentration gradient, electrophoresis of charged drugs towards an oppositely charged electrode and liberation of the entrapped drug as the gel or micelle complex erodes.

➢ CHEMICAL STIMULI INDUCED PULSATILE SYSTEMS

i. Glucose-responsive insulin release devices
In case of Diabetes mellitus there is rhythmic increase in the levels of glucose in the body, requiring injection of the insulin at proper time. Several systems have been developed which are able to respond to changes in glucose concentration. One such system includes pH sensitive hydrogel containing glucose oxidase immobilized in the hydrogel. When glucose concentration in the blood increases glucose oxidase converts glucose into gluconic acid which changes the pH of the system. This pH change induces swelling of the polymer which results in insulin release. Insulin by virtue of its action reduces blood glucose level and consequently gluconic acid level also gets decreased and system turns to the deswelling mode thereby decreasing the insulin release. Examples of the pH sensitive polymers include N, N-dimethylaminoethyl methacrylate, chitosan, polyol etc.

ii. Inflammation-induced pulsatile release:
On receiving any physical or chemical stress, such as injury, fracture etc., inflammation take place at the injured sites. During inflammation, hydroxyl radicals are produced from these inflammation-responsive cells. Degradation via hydroxyl radicals however, is usually dominant and rapid when hyaluronic acid gel is injected at inflammatory sites. Thus, it is possible to treat patients with inflammatory diseases like rheumatoid arthritis; using anti-inflammatory drug incorporated HA gels as new implantable drug delivery systems.

iii. Drug release from intelligent gels responding to antibody concentration:
There are numerous kinds of bioactive compounds which exist in the body. Recently, novel gels were developed which responded to the change in concentration of bioactive compounds to alter their swelling/deswelling characteristics. Special attention was given to antigen-antibody complex formation as the cross-linking units in the gel, since such interaction is very specific. Utilizing the difference in association constants between polymerized antibodies and naturally derived antibodies towards specific antigens, reversible gel swelling/deswelling and drug permeation changes occurs.

III. EXTERNAL STIMULI PULSATILE RELEASE
This system was divided into three subparts and is discussed below.

i. Electro responsive pulsatile release
Electrically responsive delivery systems are prepared from polyelectrolytes (polymers which contain relatively high concentration of ionisable groups along the backbone chain) and are thus, pH-responsive as well as electro-responsive. Examples of naturally occurring polymers include hyaluronic acid, chondroitin sulphate, agarose, carbomer, xanthan gum and calcium alginate. The synthetic polymers are generally acrylate and methacrylate derivatives such as partially hydrolyzed polyacrylamide, polydimethylaminopropyl acrylamide.

ii. Magnetically induced pulsatile release
Magnetic carriers receive their magnetic response to a magnetic field from incorporated materials such as Magnetite, Iron, Nickel, Cobalt etc. For biomedical applications, magnetic carriers must be water-based, biocompatible, non-toxic and non-immunogenic. Mechanistic approach based on magnetic attraction is the slowing down of oral drugs in the gastrointestinal system. This is possible by filling an additional magnetic component into capsules or tablets. The speed of travel through the stomach and intestines can then be slowed down at specific positions by an external magnet, thus changing the timing and/or extent of drug absorption into stomach or intestines.27,29,32

IV. PULSATILE RELEASE SYSTEMS FOR VACCINE AND HORMONE PRODUCTS
PDDS offer the possibility of single-shot vaccines if initial booster release of the antigen can be achieved from one system in which timing of booster release is controlled. It was found that in nutritionally anoestrous cows, GnRH administered in pulses of 2 mg over 5 min every hour for 13 days produced a higher frequency of luteal activity by 13th day than cows given continuous infusions or pulses every 4 Hrs.24

CONCLUSION
Chronotherapeutics is the discipline concerned with the delivery of drugs according to inherent activities of a disease over a certain period of time. Chronotherapy can particularly benefit patients suffering from allergic rhinitis, rheumatoid arthritis and related disorders, asthma, cancer, cardiovascular diseases, and peptic ulcer disease.

REFERENCES
PULSATILE DRUG DELIVERY

Time Controlled System

Site Specific System

Single unit system

Multiple unit system

Tablet
E.g. Time clock system

Capsule
E.g.: Pulsincap system

Pellets
E.g. Time-Controlled Explosion System

Figure 4: Classification of pulsatile drug delivery system.