ABSTRACT

Chronotherapeutics is a method of treatment in which in-vivo drug availability is timed to match rhythms of disease, in order to optimize therapeutic outcomes and minimize side effects. Pulsatile delivery system aims to release drugs in planned pattern which means at appropriate time or at appropriate site. Several controlled release preparations are available which maintains constant drug concentration in the blood and tissues but it is not desired all the time as it has some side effects such as resistance, tolerability and drug side effects. For preparing pulsatile delivery system, various design strategies have been proposed, most of them are time controlling, stimuli induced, externally regulated and multiparticulate formulations. Pulsatile delivery system is very much useful in case of drugs having chronopharmacological behavior, for the drug having high first pass metabolism effect and for those drugs which have specific site of adsorption in the GIT. The present article covers findings about the diseases which follows circadian rhythm and can be treated effectively by pulsatile delivery system. Here we also covered various methods of novel pulsatile drug delivery systems that might be able to release the therapeutic agents after proper lag time and at specific site of action.

KEYWORD: Pulsatile DDS, Drug release, Circadian rhythm.

INTRODUCTION

Now a day, the emphasis of pharmaceutical researchers is turned towards the development of more efficacious drug delivery system with existing API. Modified release dosage forms have great importance in this field. Such system controls the release pattern of drug either in control or variable rates with predetermined released rates. There are certain conditions for which such release pattern is not suitable. These condition demand release of drug after lag
time. This condition is achieved by pulsatile drug delivery system.\textsuperscript{[1]} Since many diseases exhibit predictable cyclic rhythms, the timing of medication can be used to improve the chronic condition for patients. Thus, after understanding the disease physiology an advanced drug delivery system with pulsatile function may be applied as a part of the treatment. The pulsatile drug delivery system (PDDS) is intended to deliver a rapid and quantified medication released after a predetermined off released period that is lag time. PDDS can deliver the correct amount of medication at the desired location at the optimal time for maximum effect against disease, thereby enhancing therapeutic efficacy and improving patient compliance.\textsuperscript{[2]} Many diseases show circadian rhythms in their pathophysiology. It is observed that diseases have predictable cyclic rhythms and that the timing of medication regimens can improve outcome in selected chronic conditions. For understanding concept of chronotherapeutics, it is necessary to understand following concepts:

- **Chronobiology**: It is the science concerned with the biological mechanism of the diseases according to a time structure.

- **Chronopharmacology**: Chronopharmacology is the science concerned with the variations in the pharmacological actions of various drugs over a period of time.

- **Chronopharmacokinetics**: Chronopharmacokinetics involves study of changes in drug absorption, distribution, metabolism and excretion. Pharmacokinetic parameters, which are conventionally considered to be constant in time, are influenced by different physiological functions displaying circadian rhythm. Circadian changes in gastric acid secretion, gastrointestinal motility, gastrointestinal blood flow, drug protein binding, liver enzyme activity, renal blood flow and urinary pH can play role in time dependent variation of drug plasma concentrations.

- **Chronotherapy**: Co-ordination of biological rhythms and medical treatment is called chronotherapy.

- **Chronotherapeutics**: Chronotherapeutics is the discipline concerned with the delivery of drugs according to inherent activities of a disease over a certain period of time. It is becoming increasingly more evident that the specific time that patients take their medication may be even more significant than was recognized in the past. Chronopharmaceutics consist of two words chronobiology and pharmaceutics. Chronobiology is the study of biological rhythms and their mechanisms.\textsuperscript{[2]}
There are three types of mechanical rhythms in our body.

- **Circadian**
  This word comes from Latin word circa means about and dies means day.

- **Ultradian**
  Oscillation of shorter duration is termed as ultradian (more than one cycle per 24h) less than one cycle per day.

- **Infradian**
  Oscillations that is longer than 24 h (less than one cycle per day).\(^3\)

![Fig.1 A 24-hrs clock diagram of the peak time selected human circadian rhythms with reference to the day-night cycle.\(^3\)](image)

**Examples of some of the diseases are shown in Table**

**Table 1. Circadian rhythm and manifestation of clinical diseases**\(^4\)

<table>
<thead>
<tr>
<th>Sr.No</th>
<th>Disease or syndrome</th>
<th>Circadian rhythmicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Allergic Rhinitis</td>
<td>Worse in the morning/upon rising</td>
</tr>
<tr>
<td>2</td>
<td>Asthma</td>
<td>Exacerbation more common during the sleep period</td>
</tr>
<tr>
<td>3</td>
<td>Rheumatoid Arthritis</td>
<td>Symptoms more common during the sleep period</td>
</tr>
<tr>
<td>4</td>
<td>Osteoarthritis</td>
<td>Symptoms worse in the middle/later portion of the day</td>
</tr>
<tr>
<td>5</td>
<td>Angina Pectoris</td>
<td>Chest pain and ECG changes more common in early morning</td>
</tr>
<tr>
<td>6</td>
<td>Myocardial Infarction</td>
<td>Incidence greatest in early morning</td>
</tr>
<tr>
<td>7</td>
<td>Stroke</td>
<td>Incidence higher in the morning</td>
</tr>
<tr>
<td>8</td>
<td>Sudden cardiac death</td>
<td>Incidence higher in the morning after awakening</td>
</tr>
<tr>
<td>9</td>
<td>Peptic ulcer disease</td>
<td>Worse in late evening and early morning hours</td>
</tr>
</tbody>
</table>
Need of Pulsatile drug delivery

- Body function that follow circadian rhythms.
- When circadian rhythm is altered by the hormones such as rennin, aldosterone and cortisol etc. level in blood.
- When rhythmic variation seen in acid secretion in stomach, gastric emptying, and gastrointestinal blood transfusion.
- Disease like bronchial asthma, myocardial infraction, angina pectoris, rheumatic disease, ulcer, and hypertension display time dependence.
- The lag time is essential for the drugs that undergo degradation in gastric acidic medium.
- It is possible to deliver the drugs to the distal part of GIT like colon targeting with pulsatile drug delivery.
- Drugs that undergo extensive first-pass metabolism are administered successfully as pulsatile drug delivery systems.

Advantage of pulsatile drug delivery system

- Due to its ability to release drug in a burst manner, it increases absorption and bioavailability at
- Target site of absorption.
- Limit risk of mucosal irritation.
- Loss of drug by extensive first pass metabolism is prevented.
- Chronotherapy, programmed delayed release provides optimal treatment of diseases.
- No risk of dose dumping.
- Decreases drug interaction due to lower cytochrome P450 isoenzymes.
- Avoidance of undesirable side effects.
- Improved patient compliance.
- Flexibility in design.

Disadvantage of pulsatile drug delivery system

- Low drug loading capacity and incomplete release of drug.
- Higher cost of production.
- Large number of process variables.
- Lack of manufacturing reproducibility and efficacy.
- Batch manufacturing process.
- Unpredictable IVIVC.
Diseases targeted for Pulsatile Drug Delivery System

Diseases presently targeted for chronopharmaceutical formulations are those for which there are enough scientific backgrounds to justify PDDS- 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 below.

• Hypercholesterolemia
Diverse directions of circadian changes in lipid fractions in patients and normal subjects may contribute to alteration in the rhythmicity of other metabolisms and in the blood coagulation system, thus leading to various complications. A circadian rhythm occurs during hepatic cholesterol synthesis. Therefore, cholesterol synthesis is generally higher during the night than during daylight, the maximal production occurs early in the morning, i.e., 12 h after the last meal.

• Asthma
The chronotherapy of asthma has been extensively studied. The role of circadian rhythms in the pathogenesis and treatment of asthma indicates that airway resistance increases progressively at night in asthmatic patients. Circadian changes are seen in normal lung function, which reaches a low point in the early morning hours. As bronco constriction and exacerbation of symptoms vary in a circadian fashion, asthma is well suited for chronotherapy. Chronotherapies have been studied for asthma with oral corticosteroids, theophylline, and β2-agonists.

• Cancer
Human and animal studies suggest that 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. The blood flow to tumors was three fold greater during each daily activity phase of the circadian cycle than during the daily rest phase. The chronotherapy concept offers further promise for improving current cancer-treatment options, as well as for optimizing the development of new anticancer or supportive agents.

Need of advanced technology.[1]
• **Duodenal ulcer**
Many of the functions of the gastrointestinal tract are subject to circadian rhythms: gastric acid secretion is highest at night, while gastric and small bowel motility and gastric emptying are all slower at night. During night time, 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 at bedtime is the recommended dosage regimen for an H2 antagonist.

• **Arthritis**
The chronobiology, chronopharmacology and chronotherapeutics of pain have been extensively reviewed. For instance, there is a circadian rhythm in the plasma concentration of C-reactive protein and interleukin-6 of patients with rheumatoid arthritis. Patients with osteoarthritis tend to have less pain in the morning and more at night; while those with rheumatoid arthritis, have pain that usually peaks in the morning and decreases throughout the day. Chronotherapy for all forms of arthritis using NSAIDs such as Ibuprofen should be timed to ensure that the highest blood levels of the drug coincide with peak pain.

• **Diabetes**
The circadian variations of glucose and insulin in diabetes have been extensively studied and their clinical importance in case of insulin substitution in types I diabetes have been previously discussed. The goal of insulin therapy is to mimic the normal physiologic pattern of endogenous insulin secretion in healthy individuals, with continuous basal secretion as well as meal-stimulated secretion.

• **Neurological disorders**
As an integrative discipline in physiology and medical research, chronobiology renders the discovery of new regulation processes regarding the central mechanisms of epilepsy. Chronophysiology investigations considered at a rhythmometric level of resolution suggest several heuristic perspectives regarding (i), the central pathophysiology of epilepsy and (ii) the behavioral classification of convulsive events.

• **Cardiovascular diseases**
Several functions such as, Blood pressure (BP), heart rate, stroke volume, cardiac output, blood flow of the cardiovascular system is subject to circadian rhythms. For instance,
Capillary resistance and vascular reactivity are higher in the morning and decrease later in the day. Platelet aggregability is increased and fibrinolytic activity is decreased in the morning, leading to a state of relative hypercoagulability of the blood. It was postulated that modification of these circadian triggers by pharmacologic agents may lead to the prevention of adverse cardiac events. BP is at its lowest during the sleeping period and rises steeply during the early morning period. Most patients with essential hypertension have a similar circadian rhythm of BP as do normotensive persons, although hypertensive patients have an upward shift in the profile.[5]

Pulsatile release may be monitored by altering membrane permeability, or by coating the unit with a soluble, erodible, or rupturable membrane.

![Image](image.png)

**Fig.2: Different release patterns for various pharmaceutical dosage form.**[2]

**METHODS OF DEVELOPMENT OF PULSATILE DRUG DELIVERY SYSTEM**

Different approaches of pulsatile system are

1. **Time Controlled system**
   1.1 Pulsatile Delivery by Solubilisation or Erosion of layer
   1.2 Pulsatile Delivery by Rupture of Membrane
   1.3 Capsule Shaped Pulsatile Drug Delivery System
   1.4 Pulsatile System Based On Osmosis

2. **Internally stimuli induced system**
   2.1 Temperature–induced pulsatile release
   2.1.1 Thermo responsive hydro gel systems
   2.1.2 Thermo responsive polymeric micelle systems
2.2 Chemical stimuli induced pulsatile release
2.2.1 Glucose-responsive insulin release devices
2.2.2 PH sensitive drug delivery system
2.2.3 Inflammation-induced pulsatile release
2.2.4 Drug release from intelligent gels responding to antibody concentration

3. Externally Regulated System
3.1 Magnetic induces release
3.2 Ultrasound induces release
3.3. Electric field induces release
3.4 Light induces release

4. Multiparticulate System

1. Time Controlled system

1.1 Pulsatile Delivery by Solubilisation or Erosion of layer
In such systems the drug release is controlled by the dissolution or erosion of the outer coat which is applied on the core containing drug (Figure.3). The release of the active ingredient can be controlled by thickness and viscosity of the outer coat. The Time Clock system consists of a solid dosage form coated with lipid barriers containing carnauba wax and bees wax along with surfactants. Chronotropic system consists of a core containing drug reservoir coated by a hydrophilic polymer HPMC. System is composed of a drug-containing core and swells able polymeric coating of HPMC which slow the interaction with aqueous fluids.

![Image of delivery system with erodible coating layers]

**Fig.3: Schematic diagram of Delivery systems with erodible coating layers**

1.2 Pulsatile Delivery by Rupture of Membrane
These systems consist of an outer release controlling water insoluble but permeable coating subject to mechanically induced rupture phenomenon. The rupturing effect is achieved by
coating the individual units with effervescent or swelling agents. Water permeation and mechanical resistance of the outer membrane are major factors affecting the lag time. The lag time can be varied by varying coating thickness or adding high amounts of lipophilic plasticizer in the outermost layer.

Fig. 4: Schematic diagram of Deliver systems with rupturable coating layer

1.3 Capsule Shaped Pulsatile Drug Delivery System

This dosage form consists of an insoluble capsule body containing drug and a release controlling plug (Soluble) is fitted between immediate release compartment and pulsed release compartment. The length of plug decides lag time. When it comes in contact with aqueous fluids, the cap rapidly dissolves thereby releasing the immediate release component followed by pulsed release component. Here the plug decides lag time which is inserted in to the body. A hydrostatic pressure generate inside the capsule that is why pulsatile drug delivery achieved.

Fig. 5: Schematic diagram of Capsule shaped system provided with release controlling plug
1.4 Pulsatile System Based On Osmosis

In this System, a capsule coated with semi permeable membrane is employed. There is an insoluble plug consisting of osmotically active agent and the drug formulation inside the capsule. This system divides the capsule interior into two compartments- one for the beneficial agent and the other for the osmotically active agent. Water diffuses across the semi permeable membrane when this cap comes into contact with GI fluids and it results in increased pressure inside that ejects the plug after a predetermined lag time. Thickness of the coating decides the lag time. E.g. Ritalin (methyl phenidate) used in the treatment of attention deficit hyper active disorder (ADHD) in children.8,9

![Diagram of Osmotic Pump](Image)

**Figure 6: Osmotic Pump**

2. Internally stimuli induced system

2.1.1 Temperature–induced pulsatile release

Temperature is the most widely applied triggering signal for a variety of triggered or pulsatile drug delivery systems. The body temperature often deviates from the physiological temperature (370 C) in the presence of pathogens or pyrogens. This deviation from normal range acts as a stimulus that triggers the release of therapeutic agents from several temperature-responsive drug delivery systems. Various polymer properties, including the thermally reversible coil/globule transition of polymer molecules, swelling change of networks, glass transition and crystalline melting utilized by temperature induced triggered drug delivery systems.

2.1.2 Thermo responsive hydro gel systems

Hydro gels that undergo reversible volume changes in response to changes in temperature are known as thermo sensitive gels. In thermo-responsive hydro gel systems, hydro gels undergo
reversible volume changes in response to changes in temperature. These gels shrink at a transition temperature that is referred to the lower critical solution temperature (LCST) of the linear polymer. As it undergoes volume change, this property can be utilized to obtain a squeezing hydrogel device by positioning hydrogel within a rigid capsule. The reversible volume change of temperature-sensitive hydrogels accomplish on-off release e.g. PIPAAm cross-linked gels showed thermo-responsive, off-and-on swelling/deswelling phases and it swells below 320 C temperature, on the other side shrink above this temperature.

![Fig. 7: Structure of freely mobile linear PIPAAm grafted PIPAAm hydro gels](image)

2.1.3 Thermo responsive polymeric micelle systems

Block copolymers were prepared by development of end functionalized PIPAAm with hydrophobic polymers, such as poly (butyl methacrylate) (PBMA), polystyrene (PST) etc. In aqueous solution, block copolymers formed micellar structure (with core shell structure) below PIPAAm's transition temperature. In this system, drug is released when polymer undergoes swelling or deswelling phase in response to chemical reaction with membrane, alteration of pH and Inflammation induce.

![Fig.8: Structure of block copolymer micelles](image)
The shell was constructed from thermo responsive PIPAAm, while the core comprised of hydrophobic polymer aggregates. The PIPAAm corona exhibited a change in its hydration or dehydration properties with changing temperature.

2.2 Chemical stimuli induced pulsatile release

2.2.1 Glucose-responsive insulin release devices

These devices have been developed to respond with changes in glucose concentration in the blood. The hydro gels showed a glucose-responsive, sol–gel phase transition dependent upon the external glucose concentration. These devices also have pH sensitive hydro gel containing glucose oxidase immobilized in the hydro gel. When glucose concentration in the blood increases glucose oxidase converts glucose into gluconic acid which changes the pH of the system. This swelling of the polymer induced by this pH change 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.

2.2.2 PH sensitive drug delivery system

This system contains two components- one is of immediate release type and second is pulsed release which releases the drug in response to change in pH. As different pH environment exist at different parts of the gastrointestinal tract so this advantage is utilized by pH dependent system. By selecting the appropriate pH dependent polymers, desired drug release can be achieved at specific location. Examples of pH dependent polymers are cellulose acetate phthalate, polyacrylates, and sodium carboxymethylcellulose. These polymers are used as enteric coating materials so as to provide release of drug in the small intestine.

2.2.3 Inflammation-induced pulsatile release: Any physical or chemical stress, such as injury, fracture etc. cause inflammation at the injured sites. The inflamed responsive cells produce hydroxyl radicals. Yui and co-workers focused on the inflammatory induced hydroxyl radicals and designed drug delivery systems, which responded to the hydroxyl radicals and degraded in a limited manner. They used hyaluronic acid (HA) which is specifically degraded by the hyaluronidase or free radicals. Degradation of HA via the hyaluronidase is very low in a normal state of health. Degradation via hydroxyl radicals however, is usually dominant and rapid when HA 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.

2.2.4 Drug release from intelligent gels responding to antibody concentration

In the human body numerous kinds of bioactive compounds are exist. The change in concentration of these bioactive compounds can be detected by recently developed novel gels to alter their swelling/deswelling characteristics. Antigen antibody complex formation is of great importance as the cross-linking units in the gel due to such specific interaction. Reversible gel swelling/deswelling and drug permeation changes occurs by the utilization of the difference in association constants between polymerized antibodies and naturally derived antibodies towards specific antigens.[10]

3. Externally Regulated System

3.1 Magnetic induces release

Magnetically regulated system contains magnetic beads in the implant. Magnetic steel beads were engrafted in an ethylene and vinyl acetate (EVAc) copolymer matrix that was loaded with bovine serum albumin as a model drug. The beads oscillate within the matrix on exposure to the magnetic field, alternatively creating compressive and tensile forces. This in turn acts as a pump to push more amount of the active solute out of the matrix.

3.2 Ultrasound induces release

Ultrasound is used as an enhancer for the improvement of drug permeation through a biological barrier, such as skin, lungs, intestinal controlled drug delivery e.g. Miyazaki et al. used ultrasound to achieve up to a 27-fold increase in the release of 5-fluorouracil from an ethylene and vinyl acetate (EVAc) matrix. As degradation of biodegradable matrix was enhanced by ultrasonic exposure, the rate of drug release also increased. Increasing the strength of the ultrasound resulted in a proportional increase in the amount of 5-fluorouracil released.

3.3 Electric field induces release

As these devices use polyelectrolyte thus are pHresponsive as well as electro responsive. Polyelectrolyte contains polymers with comparatively high concentration of ionisable groups along the backbone chain. For chronotherapy, several technologies are required such as microelectronics and micromachining and potential etc. These technologies also include iontophoresis, iontophoresis and infusion pumps. Under the influence of electric field,
electro-responsive hydro gels generally bend, depending on the shape of the gel which lies parallel to the electrodes whereas deswelling occurs when the hydro gel lies perpendicular to the electrodes.

3.4 Light induces release

In this system drug delivery is regulated by the interaction between light and material and can be achieved by combining a material that absorbs light at a desired wavelength and a material that uses energy from the absorbed light to regulate drug delivery. A new class of optically active nanoparticles is developed such as Gold nanoshells which comprise of a thin layer of gold surrounding a core. Required composite material can be obtained by implanting the nano shells in a NIPAAm-co-AAM hydro gel. nanoshell when absorb the near-infrared light and convert it to heat and then temperature of composite hydro gel is raised above its lower critical solution temperature (LCST). Finally, hydro gel collapses and these results in an enhanced rate of release of soluble drug held within the matrix.[11,12]

4. Multiparticulate System

These systems consist of reservoir with either rupturable or altered permeability coating and most commonly housed in Capsular body. The purpose of designing Multiparticulate dosage form is to develop a reliable formulation that has all the advantages of a single unit formulation. A rupturable pulsatile drug delivery system consists of three components: (a) drug core (b) swelling layer comprising of a superdisintegrant and a binder (c) an insoluble water permeable polymeric coating.

Marketed preparation

Adderall XR
Avinza
Coreg CR
Focaline Xr[15,16]

SOME NOVEL MULTIPARTICULATE DRUG TECHNOLOGIES

PRODAS Technology (Programmable Oral Drug Absorption System)

PRODAS technology is a combination of both Multiparticulate and hydrophilic matrix tablet technologies in which a number of minitablets gathered in a hard gelatin capsule. The minitablets produced by direct compression of granules having active ingredients. As it combines the advantages of tableting technology within a capsule so it may be immediate
release, delayed-release and/or controlled-release drug delivery systems in single dosage form.\textsuperscript{[13,14]}

**OROS Technology**

(Osmotic-controlled Release Oral delivery System) This technology depends on osmotic pressure to give pre-programmed, controlled drug delivery to the gastrointestinal tract. The system is composed of two compartments—the drug vessel and the osmotic engine cap. When the system comes in contact with an aqueous medium, water permeates into the osmotic engine cap through rate-controlling membrane. Hydration of the osmotic engine leads to its expansion, which exerts a driving force against the ridge of the drug vessel. The two compartments separate from each other by sliding apart. After disengaging, the open mouth of the drug vessel is exposed to the fluid environment. Essential entire dose get delivered by chronoset. The vessel is made of water-impermeable ethylene-co-vinyl acetate copolymer (EVA) and the cap is made of proprietary water-permeable blends of polycaprolactone (TONE) and flux enhancers.\textsuperscript{[16]}

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![Fig.9: OROS Technology](image-url)

OROS Technology Available marketed products

- **Alpress LP** (prazosin)
- **Covera-HS** (verapamil)
- **Procardia XL** (nifedipine)\textsuperscript{[15]}

**CODAS Technology** (Chronotherapeutic Oral Drug Absorption System)

This technology is designed to delay drug release for a predetermined time to tune therapy to the body’s circadian rhythms. Again, the technology is based on polymer coated
Multiparticulate. The release controlling coating is a blend of water soluble and water insoluble polymers. When water from the gastrointestinal tract get in touch with the polymer coated beads, the water soluble polymer gradually dissolves and the drug diffuses through the resulting pores in the coating. The water insoluble polymer continues to act as a barrier maintaining the controlled release of drug.

Marketed Preparation
Verelan
PM XL capsule API- Verapamil HCl[17]

**DIFFUCAPS Technology**

DIFFUCAPS technology delivers drugs into the body in a circadian release manner. Diffucaps technology in its simplistic form involves the preparation of

1. Core of Inert particles surrounded by drug layer.
2. Customized release (CR) beads by coating immediate release (IR) particles with one or more functional dissolution rate (release) controlling polymers or waxes.
3. One or more functional polymer coated Diffucaps bead populations get combine into hard gelatin or Hydroxypropyl Methylcellulose (HPMC) capsules.

![Diffucaps-Customized Drug Release Bead](image)

**Fig.10: Diffucaps-Customized Drug Release Bead**

A layer of organic acid or alkaline buffer surrounds the beads to direct solubility of a poorly soluble drug by creating an optimal pH microenvironment. Every Diffucaps bead has an inert core enclosed by drug as well as coated with a functional polymer membrane to control the rate of drug release. The active core may be produced by granulating and milling and/or by extrusion and spheronization of API. This technology is particularly suitable for drugs that
conventionally need multiple daily doses or drugs require customized release formulations. Diffucaps can also be combined with other proprietary Pharmaceutical Technologies to optimize drug delivery.\[18\]

![Fig. 11: DIFFUCAPS bead surrounded by organic acid or alkaline buffer layer](image)

**Marketed preparation**
- Innopran XL Tablets Verapamil HCl
- Zofran Tablets Ondansetron HCl dehydrate\[15\]

**SODAS Technology (Spheroidal Oral Drug Absorption System)**
SODAS is a Multiparticulate technology that enables the production of customized dosage forms and responds directly to individual drug candidate needs. The drug loaded beads are coated with controlled release polymers (water soluble and insoluble, pH dependent or independent) to form a release rate controlling membrane. Then, the beads are filled into hard gelatin capsules for ease of administration.\[19,20\]

**RECENT ADVANCES IN THE PULSATILE DRUG DELIVERY SYSTEM**
At present, pulsatile drug delivery systems have great importance in various disease conditions specifically in diabetes where dose is suggested at different time intervals. The sub-systems, multi-particulate systems (e.g. pellets) offer various advantages over single unit. The release profile of pellets can be of any type like time dependent, pH dependent, micro flora activated system. Great interest is taken in site and time specific oral drug delivery to improve therapeutic efficacy. Gastro retentive drug delivery system is a suggestion to prolong gastric residence time, thereby targeting site-specific drug release in upper gastrointestinal (GI) tract. Floating drug delivery system (FDDS) and bio adhesive drug delivery are widely
used techniques for gastro retention. Various pulsatile technologies have been developed on the basis of methodologies as discussed previously.

1. **ACCU-BREAK Technology**
   This technology is designed to easily divisible tablets in exact smaller doses, thus dosage adjustment become easy. In ACCU-T-CR Trilayer tablets, tablet contains a controlled-release (CR) medication and/or immediate release (IR) component. It gets separated by a drug-free break layer which allows the CR dose to be divided into exact half doses.

![Fig 12:-ACCU-BREAK Technology](image)

2. **TMDS Technology**
   The Time Multiple Action Delivery System provides control release rate of multiple ingredients within a single tablet in programme manner. TMDS Technology allows for more than one active ingredient in a single tablet formulation provide multiple release profile over extended period of time.

3. **Geoclock technology**
   In this technology, chronotherapy focused press coated tablets or Geoclock tablets have an active drug inside an outer tablet layer consisting of a mixture of hydrophobic wax and brittle material in order to obtain a pH-independent lag time prior to core drug delivery at a predetermined release rate. This dry coating approach is designed to allow the timed release of both slow release and immediate release active cores by releasing the inner table first after which time the surrounding outer shell gradually disintegrates. e.g. LODOTRA – used in rheumatoid arthritis.
4. **Duredas technology** (Dual Release Drug Absorption System)
In this technology, a bilayer tablet was manufactured. One layer of the tablets provided with immediate release action and second layer with sustained release action.

5. **KV/24**
In this technology, one or more drug compounds remain encapsulated to express release of drug in a pre-determined fashion. Prior to coating with one or more polymers, a neutral core is coated with a drug substance to achieve a once-a-day release profile. The drug can be combined in two ways, one with the neutral core second incorporated into the coating process.

6. **Innoherb**
In this technology, pellets are coated inside of the capsule. Desired active herbal compound converted into micro pellets or small beads. The coating of these carried out by semi permeable membrane to improve stability and mask taste/smell.

7. **IPDAS Technology** (Intestinal Protective Drug Absorption System)
In this, the beads with high density drug are compressed to form controlled release tablets. It is particularly suitable for tablet that cause gastro irritation and disintegrates rapidly. The release is controlled by the nature of the drug-containing bead matrix or its semi-permeable membrane coating. It is extruded and spheronised Multiparticulate based technology. Initially, it was developed for a proprietary formulation of naproxen with fast onset of action to relief pain over a 24-hour period which is marketed in the US and Canada under the trade name Naprelan.

8. **Orbexa Technology**
In this multi particulate system, high drug is loaded and product is subjected to granulation. After granulation/extrusion and spheronization, functional polymer membranes are used to coat the resultant beads for additional release rate control and may be filled into capsules. This technology can be used for sensitive drugs such as proteins.

**EVALUATION PARAMETERS**

*Weight variation test*[^21]
To study weight variation 20 tablets of each formulation were weight using a electronic balance and the test was performed according to the official method.
Hardness\textsuperscript{[21]}
For each formulation, the hardness of 3 tablets was determined using the validated Pfizer and Monsanto hardness tester.

Friability\textsuperscript{[21]}
Friability was performed by using Roche friabilator; normally pre-weighed 20 tablets were placed in the plastic chamber of friabilator and then operated for 100 revolutions. Tablets dropping from a distance of six inches with each revolution. Tablets were then dusted and reweighed.

$$\text{Friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

Thickness\textsuperscript{[21]}
The thickness of the tablets was determined by using vernier caliperse. Three tablets from each formulation were used and average values were calculated.

Content Uniformity of core tablet\textsuperscript{[21]}
Ten tablets were weighted and powdered in a mortar. Accurately weighted a quantity of the powder equivalent to about 8 mg of lornoxicam, dissolved in 20 ml dimethyl formamide and the volume was adjusted to 100ml by addition pH 6.8 phosphate buffer in 100 ml volumetric flask. It was shaken for 15 minutes and filtered. 10 ml of the filtrate was diluted to 100 ml with phosphate buffer pH 6.8 in 100 ml volumetric flask. The absorbance of the resulting solution was measured at the maximum at about 376 nm. And found the amount of the lornoxicam using the calibration curve method.

Determination of tablet tensile strength\textsuperscript{[21]}
This is the stress needed to fracture a tablet by diametral compression. It is given by Fell and Newton as: $T=2P\pi Dt$ Where P is the fracture load that causes tensile failure of a tablet of diameter D, and thickness t. The fracture load (kg) of ten tablets was determined individually with a Monsanto hardness tester (Tab Machines, Mumbai, India), using the procedure of Brook and Marshal. The mean values of the fracture loads were used to calculate T values for the various tablets.

Rupture test\textsuperscript{[21]}
The lag time of pulsatile release tablets is defined as the time when the outer ethyl cellulose coating starts to rupture due to swelling. It was determined visually using 900 ml of
phosphate buffer pH 6.8, 37 ± 0.5°C, and at 50 rpm in the USP paddle type (type II) dissolution apparatus.

**Dissolution study**[22]

The USP XXIV rotating paddle method (37.0F0.5 jC, 50 rpm, 900 ml) was used to study the drug release from the pulsatile release tablets. Samples were withdrawn after predetermined time intervals and the amount of buflomedil HCl released was assayed with a spectrophotometer.

**CONCLUSION**

Rapid advancement and newer developments in the field of drug delivery has led to the formulation of the pulsatile drug delivery system, which, on one hand, can be formulated with ease and, on the other hand, provide a significant amount of therapeutic benefits. These systems deliver the drug at right time, place and amount in the patient’s body. The circadian disorders generally require chronopharmacotherapy, which can be easily accomplished by pulsatile drug delivery system in a very organized manner. During the last two decades the pharmaceutical technology has grown leaps and bounds and with the advent of pulsatile drug delivery one can remain assured of accomplishment of goal for safe and effective therapy. There are a number of ailments that require that the drug/bioactive be delivered in a specific way. The same cannot be either achieved or the benefits are partial when it comes to the conventional dosage forms Significant modification and designing of the conventional delivery systems in the form of pulsatile delivery systems ensures the time-controlled pulsatile release of bioactive compounds, which is prerequisite in the treatment of such disorders. The etiology of the dreaded diseases can be linked to the release of the specific drugs through these systems, which would definitely result in the betterment of the therapy. Although several milestones have been reached in this respect, there are still some unexplored facets of pulsatile drug delivery that can open new vistas through better engineering of the same.

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