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Review Article

# CHRONOTHERAPEUTICS: AN OPTIMIZING APPROACH TO SYNCHRONIZE DRUG DELIVERY WITH CIRCADIAN RHYTHM

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**ABSTRACT**

Drug delivery systems that precisely control the release rates or target drugs to a specific site have an enormous impact on health care system. In the modern era of treatment many new approaches have been evolved for more efficient administration of drugs. One such approach is the administration of drugs at times at which they are most effective and best tolerated. Chronotherapeutics is the approach in which *in vivo* availability of drug is timed to match rhythms of disease or disorders in order to optimize therapeutic responses and minimize side effects, which makes it a profound and purposeful delivery of medications in unequal amounts over time (during the 24h). Chrono therapeutic drug delivery systems (ChrDDS) are gaining importance in the field of pharmaceutical technology as these systems reduce dosing frequency, toxicity and deliver drug that matches the circadian rhythm (CR) of that particular disease when the symptoms are maximum to worse. Eventually, the benefit goes to the patient due the compliance and convenience of the dosage form. Various technologies such as time controlled, pulsed, triggered and programmed drug delivery devices have been developed and extensively studied in recent years for chrono pharmaceutical drug delivery. This review specially focuses on ChrDDS and various dosage forms, techniques that are used to target the CR's of various diseases.

**Keywords:** Chrono therapeutic drug delivery systems, Circadian rhythms, Therapeutic response, Time controlled, Pulsed, Triggered and programmed technologies.

## INTRODUCTION

The term "*chrono*" basically refers to the study that every metabolic happening undergoes rhythmic changes in time [1]. Chrono-therapeutics refers to a therapy in which *in vivo* availability of drug is timed to match rhythms of disease or disorders in order to optimize therapeutic responses and minimize side effects, which makes it a profound and purposeful delivery of medications in unequal amounts over time (during the 24 h) [2]. Chronotherapeutics takes into account rhythm determinants of the human circadian time structure to determine the drug-delivery pattern, dose, and administration time to optimize desired and/or minimize adverse effects [3, 4]. Circadian rhythms are self-sustaining, endogenous oscillations that occur with a periodicity of about 24 h 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.

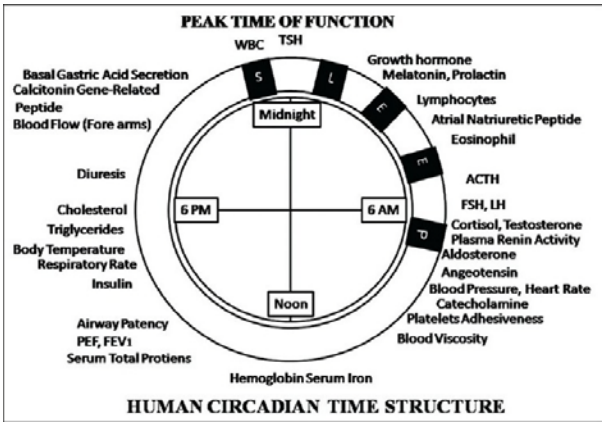


**Fig. 1: Human Circadian Time Structure; shown is the approximate peak time of the circadian (24-hour) rhythms of selected biological variables in persons adhering to a normal routine of daytime activity (6-7 a. m. to 10-11 p. m.) alternating with night time sleep**

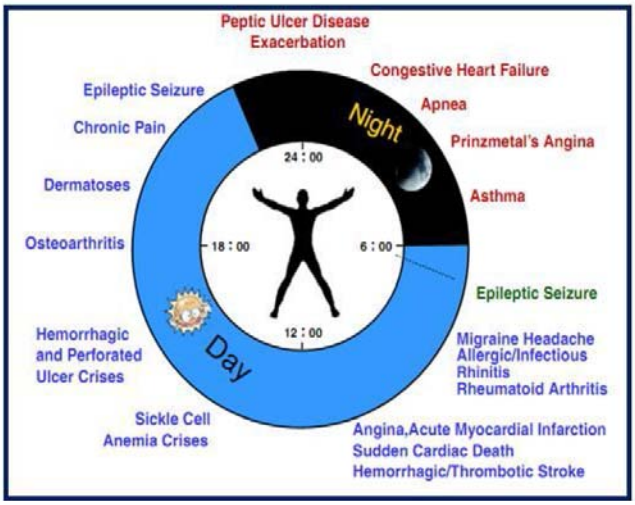


**Fig. 2: A 24 h clock diagram of the peak time of selected human circadian rhythms with reference to day-night cycle**

### Ideal characteristics of ChrDDS [5]

1. Non-toxic within approved limits of use.

2. Should have a realtime and specific triggering biomarker for a given disease state.

3. Should have a feed- back control system (e. g. self-regulated and adaptative capability to circadian rhythm and individual patient to differentiate between awake–sleep status).

4. Biocompatible and biodegradable, especially for parenteral administration.

5. Easy to manufacture at economic cost.

6. Easy to administer in to patients in order to enhance compliance to dosage regimen.

**Table 1: Diseases requiring Chronotherapeutic drug delivery**

| Disease | Chronological behavior | Drug used |
|---|---|---|
| Cardiovascular diseases | BP is at its lowest during night or at early morning awakening period | Nitroglycerin, Calcium channel blocker, ACE Inhibitors etc. |
| Diabetes mellitus | Increase in the blood sugar level after meal | Sulfonyl urea, Insulin, Biguanide |
| Asthma | Precipitation of attacks during night or at early morning hour. | $\beta_2$ agonist, Antihistaminics |
| Arthritis | Pain in the morning and more pain at night | NSAIDS, Glucocorticoids |
| Peptic ulcer | Acid secretion | H2 blockers |
| Hypercholesterolemia | Cholesterol synthesis is generally higher during night than during day time | HMG CoA reductase Inhibitors |
| Arthritis | Pain in the morning and more pain at night | NSAIDS, Glucocorticoids |

**Table 2: Drugs developed or under development as chronotherapies.**

| S. No. | Class of drugs | Examples |
|---|---|---|
| 1. | Cardiovascular drugs | Verapamil, Felodipine, Propranolol, Captopril, Metoprolol, Diltiazem, Nifedipine, Enalapril, Nitroglycerine, Dofetilide |
| 2. | Anti asthmatic drugs | Methylprednisolone, Prednisolone, Albuterol, Terbutaline, Theophylline, Montelukast sodium, Budesonide |
| 3. | Anti cancer drugs | Cisplatine, Oxaliplatine, Doxorubucin, 5-fluorouracil, Folinic acid, Methotrexate, Mercaptopurine |
| 4. | NSAIDs | Diclofenac sodium, Ibuprofen, Ketoprofen, Oxymorphone, Indomethacin, Tenoxicam, Acetyl salicylic acid |
| 5. | Diabetes mellitus | Sulphonyl urea, Insulin |
| 6. | Anti ulcer drugs | Cimetidine, Ranitidine, Famotidine, Pirenzipine, Omeprazole |
| 7. | Anti cholesterolemic drugs | Simvastatin, Lovastatin |
| 8. | Irritable bowel disease | 5-amino salicylic acid |
| 9. | Others | Amoxycilline, Vitamin $D_3$, Diazepam, Haloperidol, Methylphenidate |

**Advantages [6, 7]**

- Predictable, reproducible, and short gastric residence time.
- Less inter-and intra-subject variability.
- Improves bioavailability.
- Reduced adverse effects and improved tolerability.
- Limited risk of local irritation.
- No risk of dose dumping.
- Flexibility in design.
- Ease of combining pellets with different compositions or release patterns
- Improves stability.
- Improves patient comfort and compliance.
- Achieves a unique release pattern.
- Extends patent protection, globalizes the product, and overcomes competition.

**Disadvantages**

- Low drug loading.
- Proportionally higher need for excipients.
- Lack of manufacturing reproducibility and efficacy.
- Large number of process variables.
- Multiple formulation steps.
- Higher cost of production.
- Need of advanced technology.
- Trained/skilled personnel were needed for manufacturing.

**Classification of pulsatile drug delivery systems**

**I. Time controlled pulsatile drug delivery**

**A. Single unit pulsatile systems**

*Capsule based system:* Single-unit systems are mostly developed in capsule form. Pulsincap (fig. 4) is a system that comprises of a water-insoluble capsule enclosing the drug reservoir. When this capsule comes in contact with the dissolution fluid, the polymer plug (E. g. polymethacrylates, hydroxypropylmethyl cellulose, polyvinyl alcohol, Polyethylene oxide, saturated polyglycolated glycerides, glyceryl monooleate, pectin) swells; and after a lag time, the plug pushes itself outside the capsule and the drug is released rapidly [9].

**Drug release profiles from pulsatile drug delivery system [8]**

Drug release profile from pulsatile drug delivery system is given fig.3.

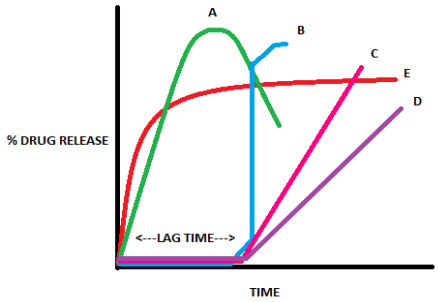


**Fig. 3: Drug release profiles from pulsatile drug delivery system**

Where, A: Conventional release profile, B: Burst release of drug as a after a lag time, C: Delayed release profile after a lag time, D: Constant release profile in prolonged period after a lag time, E: Extended release profile without lag time.

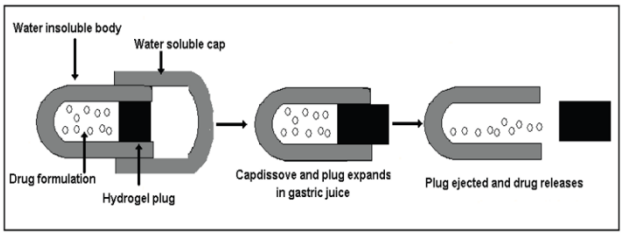


**Fig. 4: Pulsincap system**

**1) Capsular system based on osmosis**

**I. 'PORT' system**

The Port system (fig. 5) consists of a capsule coated with a semi permeable membrane. Inside the capsule was an insoluble plug consisting of osmotically active agent and the drug formulation. When this capsule comes in contact with the dissolution fluid, the

semipermeable membrane allows the entry of water, which causes the pressure to develop and the insoluble plug is expelled after a lag time [10].

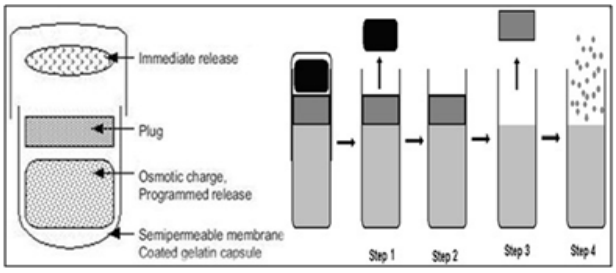


**Fig. 5: PORT system**

· Step1: Cap dissolves off. Immediately or modified release dose is released.

· Step2: Energy source is activated by controlled permeation of GI fluid.

· Step 3: Time-release plug is expelled.

· Step 4: Pulse or Sustained release of second dose.

### II. System based on expandable orifice

This system is suitable for insoluble drugs, Polypeptides and Polysaccharides [11] absorbed into highly porous particles by the capsule's osmotic infusion of moisture from the body (fig. 6). The capsule wall is made up of an elastic material (eg. elastomers, such as styrene-butadiene copolymer) and possesses an orifice. As the osmosis proceeds, the pressure within the capsule rises, causing the wall to stretch. When the elastic wall relaxes, the flow of the drug through the orifice essentially stops, but when the elastic wall is distended beyond the threshold value, the orifice expands sufficiently to allow drug release at a required rate. Pulsatile release was achieved after lag times of 1 to 10 h [12].

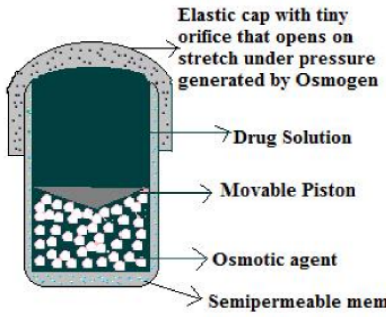


**Fig. 6: System based on expandable orifice**

### III. Delivery by a series of stops

This system is for implantable capsules. The capsule contains a drug and the water-absorptive osmotic engine that are placed in compartments separated by a movable slider that provides pulsatile release of drug. Series of stops obstruct the movement of the drug and provides lag time which is overcome as the osmotic pressure rises above a threshold level [13].

### IV. Delivery by solubility modulation

This system was especially developed for delivery of salbutamol sulphate that contained sodium chloride as modulating agent. Amount of NaCl 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. Ratio of drug/modulator may be varied to control zero order release period and commence pulsed release. After the period of zero-order release, the drug is delivered as one large pulse [14, 15].

### 2) 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 rapidly from reservoir core. The lag time depends on the thickness of the coating layer.

### i. The Chronotropic system

The Chronotropic system (fig. 7) consists of a drug containing core coated by hydrophilic swellable HPMC that produces lag phase [16]. The variability in gastric emptying time can be overcome by application of an outer enteric film, and a colon-specific release can be obtained [17]. The lag time is controlled by the thickness and the viscosity grades of HPMC [18].

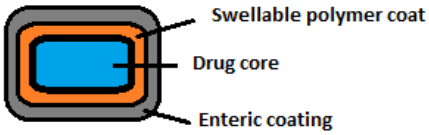


**Fig. 7: The chronotropic system**

### ii. Time clock system

The time clock system is a delivery device based on solid dosage form that is coated by an aqueous dispersion. The core is coated at 75 °C with aqueous dispersion of a hydrophobic surfactant layer (Beeswax, carnubawax, poly {oxyethylene}-sorbiton monooleate) [19]. A water soluble coat is applied to improve adhesion to the core coat (fig. 8). Once in contact with the dissolution fluid, the dispersion rehydrates and redisperses. After the lag time, the core immediately releases the drug [20].

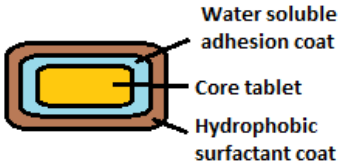


**Fig. 8: Time clock system**

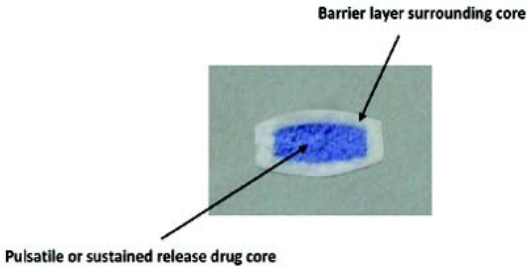


**Fig. 9: Compressed tablets**

### iii. Compressed tablets

Compression coating involves direct compression of both the core and the coat, averting needs for use of coating solutions. The outer tablet of the compression-coate d 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. Cellulose derivative may be used for this purpose [21, 22].

### iv. Multilayered tablets

Two pulses can be obtained from a three layered tablet containing two drugs containing layers separated by a drug-free gellable polymeric barrier layer (fig. 10). This three-layered tablet is coated

on three sides with impermeable ethyl cellulose, and the top portion was left uncoated. Upon contact with the 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 [23].

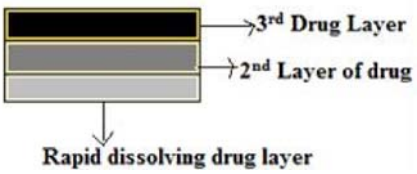


**Fig. 10: Multilayered tablet**

### 3) Pulsatile system with rupturable coating

These systems depend on disintegration of the coat for the release of drug. The pressure needed for the rupture of the coating is achieved by effervescent excipients, swelling agents, or osmotic pressure. An effervescent mixture of citric acid and sodium bicarbonate incorporated in a tablet core coated with ethyl cellulose produced carbon dioxide after penetration of water into the core resulting in pulsatile release of drug after rupture of the coat [24, 25].

### B. Multiparticulate/Multiple unit systems

#### (1) Pulsatile system based on rupturable coating

*Time-controlled expulsion system (TCES):* fig. 11 Multiparticulate system where drug is coated on non-pareil sugar seeds followed by a swellable layer (sodium carboxymethyl cellulose, sodium starch glycollate, L-hydroxypropyl cellulose, polyvinyl acetate, polyacrylic acid, polyethylene glycol, etc.) and an insoluble top layer coating [26]. Alternatively, effervescent system comprising a mixture of tartaric acid, citric acid and sodium bicarbonate may also be used. Upon ingress of water, the swellable layer expands, resulting in rupture of film with subsequent rapid drug release. The lag time can be varied by varying coating thickness or adding high amounts of lipophilic plasticizer in the outermost layer. A rapid release after the lag phase can be achieved with increasing concentration of osmotic agent [27].

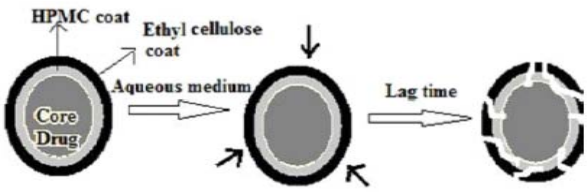


**Fig. 11: Time-controlled expulsion system**

#### (2) Osmotic based rupturable coating system

This system is based on a combination of osmotic and swelling effects. The core contains drug, a low bulk density solid and/or liquid lipid material (eg, mineral oil) and a disintegrant. The core is finally coated with cellulose acetate. Upon immersion in aqueous medium, water penetrates the core displacing lipid material. After the depletion of lipid material, internal pressure increases until a critical stress is reached, which results in rupture of coat [28].

#### (3) Pulsatile Delivery by Change in Membrane Permeability

Polymer-Eudragit. Its positively polarized quarternary ammonium group being hydrophilic facilitates the interaction of polymer with water, thereby changing its permeability and allowing water to permeate the active core in a controlled manner. This property is essential to achieve a precisely defined lag time. The cores were prepared using theophylline as model drug and sodium acetate. These pellets were coated using Eudragit in four different layer thicknesses. It was found that the amount of sodium acetate in the pellet core had a dramatic effect on the drug permeability of the Eudragit film. After the lag time, interaction between the acetate and polymer increases the permeability of the coating so significantly that the entire active dose is liberated within a few minutes [29].

#### (4) Sigmoidal release system

This consists of the pellet containing drug and succinic acid coated with ammonio-methacrylate copolymer. The water in the medium dissolves succinic acid. The drug inside and the acid solution increase the permeability of the polymer film. Instead of succinic acid, acetic acid, glutaric acid, tartaric acid, malic acid, or citric acid is also used. This system was used to design an acid containing core [30, 31].

#### (5) 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.

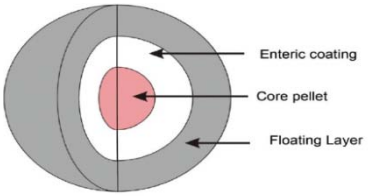


**Fig. 12: Low density floating multiparticulate system**

### ii. Stimuli induced pulsatile systems

#### (1). Temperature induced systems

Thermo-responsive hydrogel systems have been developed for pulsatile release. In these systems, the polymer undergoes swelling or deswelling phase in response to the temperature which modulate drug release in swollen state [32].

#### (2). Chemical stimuli induced pulsatile systems

**a). Glucose responsive insulin release devices:** It 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 des welling mode thereby decreasing the insulin release. Examples of the pH sensitive polymers include N, N di methyl aminoethyl methacrylate, chitosan, polyol etc.

**b). Inflammation-induced pulsatile release***:* On receiving any physical or chemical stress, such as injury, fracture etc., and inflammation takes place at the injured sites. During inflammation, hydroxyl radicals are produced from these inflammation-responsive cells. Hyaluronic acid (HA) is specifically degraded by the hyaluronidase or free radicals. 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 [33].

**c). Drug release from intelligent gels responding to antibody concentration**

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, 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[32, 33].

**d). pH sensitive drug delivery system**

This type of pulsatile drug delivery system contains two components. The first is fast release type while the other is pulsed release which releases the drug in response to change in pH. In case of pH dependent system, by selecting the pH dependent polymers, eg's: cellulose acetate phthalate, polyacrylates, and sodium carboxymethylcellulose (enteric coating materials for drug release in small intestine) drug release at specific location of the gastrointestinal tract can be obtained [32].

**III. Externally regulated pulsatile drug delivery**

**(1). Ultrasound based drug delivery systems**

Ultrasound is an enhancer for improvement of drug penetration through biological barriers such as skin, blood vessels etc. The ultrasound effect enhances degradation of the polymer in which the drug molecules are incorporated. The drug can be released by repeated ultrasound exposure. Pulse delivery is achieved by on-off application of ultrasound [34, 35].

**(2). Magnetic based drug delivery systems**

Magnetically regulated system contains magnetic beads in the implant. On application of the magnetic field, drug release occurs because of magnetic beads. Magnetic carriers receive their magnetic response to a magnetic field from incorporated materials in beads such as magnetite, iron, nickel, cobalt etc [36].

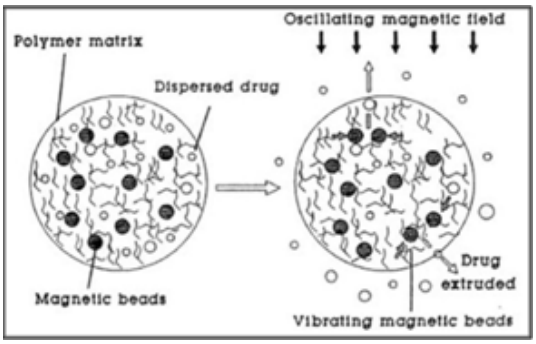


**Fig. 13: Magnetic based drug delivery systems**

**(3). Electric based drug delivery systems system**

Electrically responsive delivery systems are prepared by polyelectrolytes (polymers which contain the relatively high concentration of ionisable groups along the backbone chain) and are thus, pH-responsive as well as electro-responsive. Under the influence of electric field, electro responsive hydrogels generally bend, depending on the shape of the gel which lies parallel to the electrodes whereas deswelling occurs when the hydrogel lies perpendicular to the electrodes [37].

**(4). Radiation based drug delivery systems**

The interaction between light and material can be used to modulate drug delivery. This can be accomplished by combining a material that absorbs light at a desired wavelength and a material that uses energy from the absorbed light to modulate drug delivery. Light-sensitive hydrogels have potential applications in developing optical switches, display units, and opthalmic drug delivery devices [38].

**Classification of ChrDDS technologies based on route of administration**

**I. Chronomodulated systems for oral route**

**CODAS® (Chrono therapeutic Oral Drug Absorption System)**

Developed by Elan Corporation, USA. It is a multiparticulate system, dosed at bed time that delays drug release for 4-5 h. The delay is provided by the level of release controlling polymer (a combination of water soluble and water-insoluble polymers) applied to the drug-loaded beads. The technique has been used in formulation of Verapamil extended release capsules Verelan® PM [39].

**Contin® technology**

Developed by Purdue Pharma. Molecular coordination complexes are formed between a cellulose polymer and a non-polar solid aliphatic alcohol optionally substituted with an aliphatic group by solvating the polymer with a volatile polar solvent and react the solvated cellulose polymer directly with the aliphatic alcohol, preferably as a melt. This constitutes the complex having utility as a matrix in controlled release formulations since it has a uniform porosity (semi permeable matrixes) that may be varied [40].

**Ceform® technology**

This technique helps in development of microspheres of uniform size and shape. It is based on "melt spinning" in which biodegradable polymer or bioactive agents combination is subjected to the combination of temperature, thermal gradients, mechanical forces, flow, and flow rates during processing. The microspheres can be used in tablet capsule, suspension, sachet form. It can also be coated for controlled release [8].

**Diffucaps® technology**

Developed by Eurand Pharmaceuticals Ltd, USA. Diffucaps is a multiparticulate bead system comprised of multiple layers of drug, excipients, and functional polymer membrane to control the rate of drug release. Diffucaps beads are<1.5 mm in diameter and can be filled into capsules. The beads contain a layer of organic acid or alkaline buffer to control the solubility of a drug by creating an optimal pH microenvironment for drugs that exhibit poor solubility in intestinal pH, in environments with pH greater than 8.0, or in physiological fluids [41].

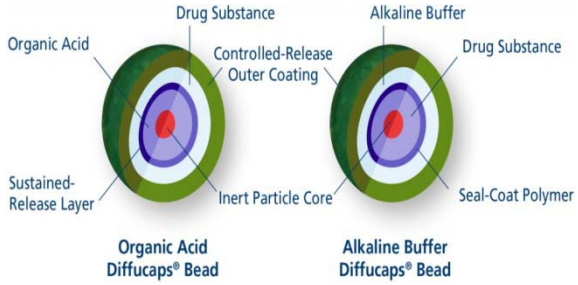


**Fig. 14: Diffucaps® technology**

**Diffutab®**

The Diffutab technology incorporates a blend of waxes and hydrophilic polymers that control drug release through diffusion and erosion of a matrix tablet. Diffutabs are particularly useful for high dose products. This technology is applies to both soluble and insoluble products [43].

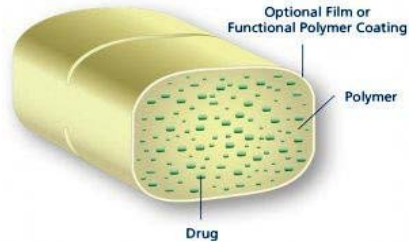


**Fig. 15: Diffutab® technology**

**Egalet® technology**

Developed by Egalet Ltd, Denmark. System consists of an impermeable shell with two lag plugs; active drug is sandwiched between the plugs. After the inert plugs have eroded, the drug is

released, thus a lag time occurs. This system shows erosion control drug release [42].

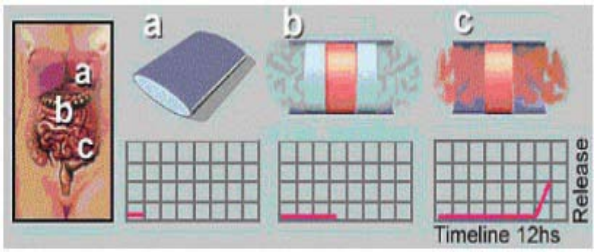


**Fig. 16: Egalet® Technology**

a. Egalet® tablet b. Erosion of an outer layer of matrix c. Release of drug after a lag period

**Geoclock®technology**

Developed by Skye Pharma. 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 tablet first after which time the surrounding outer shell gradually disintegrates [44].

**Geomatrix™ technology**

Developed by Skye Pharma Plc., USA. It is multi layered tablet which consists of a hydrophilic matrix core, containing the active ingredient and one or two impermeable or semi-permeable polymeric coatings (films or compressed barriers) applied on one or both bases of the core which act as surface controlling barriers [45, 46].

**IPDAS® *(Intestinal Protective Drug Absorption System)***

The IPDAS technology is composed of numerous high-density, controlled release beads, which are compressed into a tablet form. Once an IPDAS tablet is ingested, it disintegrates and disperses beads containing a drug in the stomach, which subsequently passes into the duodenum and along the gastrointestinal tract in a controlled and gradual manner, independent of the feeding state. The intestinal protection by this technology is due to the multiparticulate nature of the formulation, which ensures wide dispersion of irritant drug throughout the gastrointestinal tract [47].

**Intellimatrix™ technology**

Intelli Pharmaceutical Company have developed Novel oral Time controlled Release Matrix tablet Known as IntelliMatrixTM tablet. IntelliMatrixTM drug delivery platform is the unique composition of several different 'intelligent' polymers such as hydroxy ethyl cellulose and a channel former as Lactose. IntelliMatrixTM system is at the heart of proprietary drug delivery.

**Eurand minitabs® technology**

Developed by Aptalis Pharmaceutical Technologies. It consists of tiny (2 mm x 2 mm) cylindrical tablets coated with a functional membrane to control the rate of drug release. They contain gel-forming excipients that control the drug release rate. The tablets are filled into capsules, allowing a combination of multiple drugs and/or multiple release profiles in the same dosage form. Minitabs can be formulated as matrix tablets prior to further coating [48].

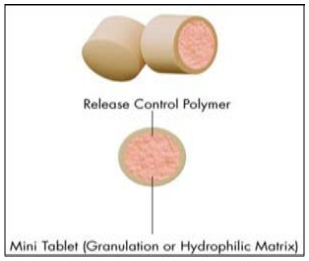


**Fig. 17: Minitabs® technology**

***Orbexa®***

Developed by Aptalis Pharmaceutical Technologies**.** Orbexa technology is a multiparticulate system that enables high drug loading and is suitable for products that require granulation. This technology consists of beads of a controlled size and density using granulation/extrusion and spheronization techniques. These beads provide higher drug concentration, can be coated with functional polymer membranes for additional release rate control and can also be used for sensitive drugs such as proteins, enzymes [49].

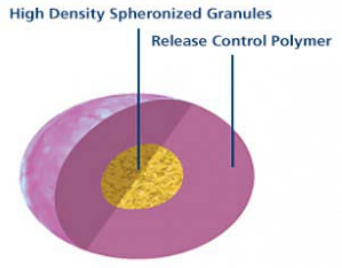


**Fig. 18: Orbexa® technology**

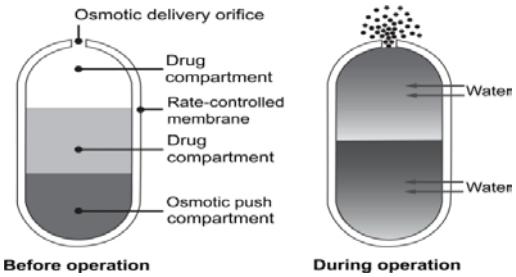


**Fig. 19: OROS® technology**

**OROS technology**

This technology uses osmotic agents to provide pre programmed, controlled drug delivery to the gastrointestinal tract This technology, especially the OROS® delayed push pull™ system, also known as controlled onset extended release (COER) was used to design covera-HS®, a novel antihypertensive product. This enables delay, overnight release of verapamil to prevent surge in BP in morning [8].

**PORT technology**

A water permeable coated gelatin capsule with osmotic core that swells and is sealed with an insoluble wax plug. The content swells to remove the plug. The wall thickness and composition, concentration of the osmotic contents and the length of the hydrogel plug control lag time.

**Eurand's pulsatile and chrono release system**

Eurand's time controlled pulsatile release system is capable of providing one or more rapid release pulses at predetermined lag times, such as when Chronotherapy is required, and at specific sites, such as for absorption along the GI tract. These capabilities can help optimize efficacy and/or minimize side effects of a drug substance.

**PRODAS® technology**

Programmable Oral Drug Absorption System (PRODAS® Technology) is a multiparticulate technology, which is unique in that it combines the benefits of tabletting technology within a capsule. The PRODAS® delivery system is presented as a number of mini tablets combined in a hard gelatin capsule. Very flexibly, it can be used to pre-program the release rate of a drug [50].

**Pulsincap™ technology**

Pulsincap (R) is an oral drug delivery device which is designed to release the drug in a pulsed fashion at a predetermined time in the gastrointestinal tract or at a predetermined site in the body. This

dosage form consists of a capsule composed of a water insoluble body and a water soluble cap. The drug formulation is contained within the capsule body and is sealed in by a hydrogel plug. At a specified time after ingestion, the drug is released into the small intestine or colon for absorption into the blood stream.

**Pulsys™ technology**

The PULSYS™ dosage form is a compressed tablet that contains pellets designed to release drug at different regions in the gastrointestinal tract in a pulsatile manner. The dosage form is made up of multiple pellet types of varying release profiles that are combined in a proportion so as to produce a constant escalation in plasma drug levels in the early portion of the dosing interval. The transit properties of pellets enhance the overall absorption-time window and offer improved bioavailability compared to tablet matrix forms [51].

**SODAS® (Spheroidal Oral Drug Absorption System)**

Developed by Elan Corporation. Multiparticulate drug delivery system, consist of uniform spheroidal beads of 1-2 mm in diameter. Each bead begins as an inert core onto which the drug is applied, followed by a number of layers of soluble and insoluble polymers combined with other excipients to produce the rate-controlling layer. Drug release from these beads occurs by a diffusion process. Within the GI tract, the soluble polymers dissolve, leaving pores within the outer membrane. Fluid then enters the core of the beads and dissolves the drug. The resultant solution diffuses out in a controlled, predetermined manner allowing for prolongation of the *in vivo* dissolution and absorption phases. These controlled-release beads can be packaged into a capsule or compressed into a tablet to produce the final dosage form [52].

**Three dimensional printing technology**

Three dimensional printing (3DP) is a novel solid free form fabrication technology that has been applied to the fabrication of complex pharmaceutical drug devices, or three-dimensional printing (3DP) is a rapid prototyping (RP) technology. Prototyping involves constructing specific layers that use powder processing and liquid binding materials [50].

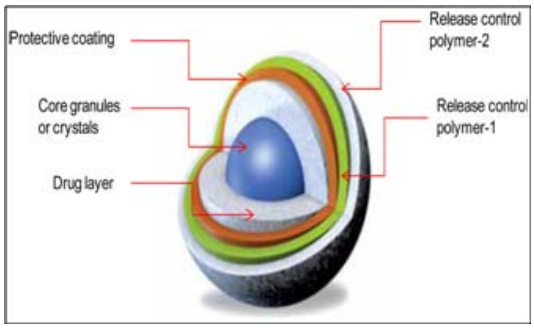


**Fig. 20: SODAS® technology**

**Timerx® technology**

This technology uses the combination of xanthan gum and locust bean gum mixed with dextrose. The physical interaction between these components works to form a strong binding gel in presence of water. Release of the drug is controlled by rate of water penetration from GIT to the above mentioned gum matrix, which expands to form a gel and releases active drug substance [8].

**II. Chronomodulated systems for transdermal route**

***Crystal reservoir system***

Crystal Reservoir Technology is small patches, which shows controlled and sustained drug release. Release of a drug is based on the oversaturation of an adhesive polymer with drug, thus forcing a partial crystallization of the drug. As the skin absorbs the molecular solute, crystals re-dissolve to maintain maximum thermodynamic activity at the site of contact. By modifying the concentration of crystals to solute, various patterns of drug release are achieved [53, 54].

**Chronodose™ system**

ChronoDose (TM) is a miniaturized and automated, fully programmable, non-invasive drug delivery device. It is worn like a wristwatch and programmed like an alarm clock, to accurately and automatically deliver predefined-sized doses to coincide with peak disease symptoms. It administers higher doses automatically when disease symptoms statistically peak and less when symptoms are lighter. Chrono Dose (TM) is the next generation in "smart" transdermal drug delivery systems [55].

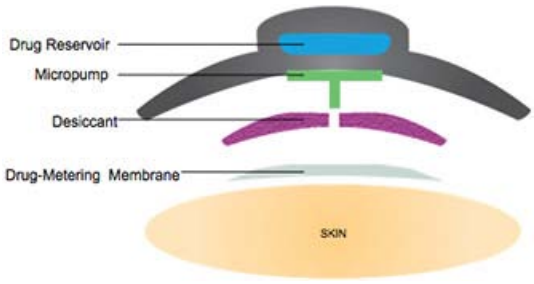


**Fig. 21: Chronodose™ System**

**Chemical oscillator**

The strategy for development of Chemical oscillator systems is based on the observation that a drug may be rendered charged or uncharged relative to its pKa value. Since only the uncharged form of a drug can permeate across lipophilic membranes, including the skin, a periodic delivery profile may be obtained by oscillating the pH of the drug solution.

The pH oscillators consist of those oscillating chemical reactions in which there is a large amplitude change in the pH. The pH of a solution can be oscillated between pH 2 to pH 10 by the redox reactions of salts, such as permanganates, iodates, sulfates, chlorates, or bromates.

The implementation of this concept (fig. 24), to a transdermal delivery system was described in U. S. Patent [56]. The user-activated system is a two chamber reservoir system, such that the compartments are separated by a weak seal during storage. The drug can be in either compartment, provided that the drug is stable in that environment. The user activates the system, prior to usage, by breaking the weak seal. The contents from the two compartments are mixed to form the pH-oscillating solution. The uncharged state of the drug then permeates across lipophilic barriers, such as the control membrane of the delivery system and skin. The use of a lipophilic control membrane ensures that the reactants, which are charged species, do not diffuse out of the drug delivery system thereby eliciting adverse biological responses.

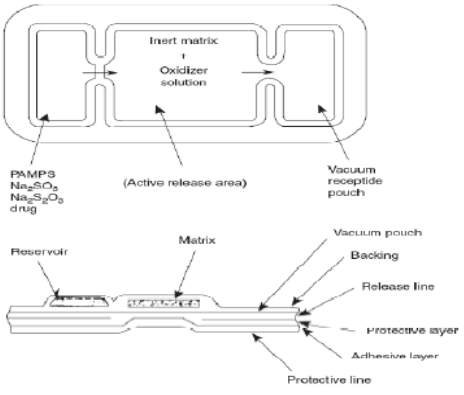


**Fig. 22: User activated system based on chemical oscillator**

**III. Chronomodulated delivery systems by implant route**

**Chronomodulated infusion pumps**

These pumps are usually characterized by a lightweight (300–500 g). Implantable infusion pumps used in Insulin therapy containing a reservoir of insulin may be surgically placed within the subcutaneous tissue of the abdomen in the left upper or lower quadrant (above or below the belt). A catheter leads from the pump through the muscle layers into the peritoneal cavity where it floats freely and insulin delivery is by intra peritoneal route. The insulin reservoir is refilled after 1 or 3 mo by inserting the needle through skin into pump. Examples of infusion pumps are Melodie®, programmable Synchromed®, Panomat® V5 infusion and the Rhythmic® pumps [57].

**Microfabrication**

These devices contain small reservoirs loaded with drugs and separated from an outside environment by the thin membrane. The active silicon-based microchip membrane is thin layer of gold. In order to release the drug the voltage need to be applied**.** The release mechanism is based on the electrochemical dissolution of thin anode membranes covering microreservoirs filled with chemicals in solid, liquid or gel form. Here a solid-state silicon microchip that can provide controlled release of single or multiple chemical substances on demand [58].

**Magnetic nanocomposite hydrogel**

Magnetic nanocomposite of temperature responsive hydrogel was used as remote controlled pulsatile drug delivery. Nanocomposites were synthesized by incorporation of superparamagnetic $Fe_3O_4$ particles in negative temperature sensitive poly (N-Nisopropylacrylamide) hydrogels.

High frequency alternating magnetic field was applied to produce on demand pulsatile drug release from nanocomposite hydrogel. Nanocomposite hydrogels temperature increase above LCTS so, result in to accelerated collapse of gel. Hence Nanocomposite hydrogels are one type of On-Off device where drug release can be turn on by application of alternative magnetic field [59].

**Hurdles in ChrDDS research and development [60, 61]**

Currently there are three major hurdles for the successful transition of ChrDDS from laboratory to market.

**a) Rhythmic biomaterials and systems**

There have been good advancement of systems intended for chrono therapy but the true burst through in this field will only be possible with smarter biomaterials. Advances in microfabrication, nanotechnology, and polymer chemistry in near future will augment the development of such material.

**b) Rhythm engineering and modeling**

The second major hurdle to chrono pharmaceutical drug formulation is ability to engineer rhythm and use reliable models, to predict the complex physicochemical properties of these novel delivery systems as well as their biological responses.

**c) Regulatory issues**

The regulatory agency evaluates NDDS formulations with greater stringency especially for validations, stability and facility to ascertain the product design ruggedness and biological performance. Establishing therapeutic efficacy requires new testing techniques both analytically and biologically is another challenge. As a whole, developing a commercially successful NDDS poses many challenges.

**Table 3: Marketed technologies of Chronotherapeutic drug delivery**

| Technology | Mechanism | API | Disease | Proprietary name |
|---|---|---|---|---|
| CODAS® | Multiparticular pH dependent | Verapamil Hcl | Hypertension | Verelan® PM |
| CONTIN® | Extended release tablet | Theophylline | Asthma | Uniphyl® |
| CEFORM® | Extended release tablet | Diltiazem HCl | Hypertension | Cardiazem® |
| Diffucaps® | Multiparticulate | Verapamil HCl, Propranolol HCl | Hypertension | Innopran® |
| Geoclock™ | Chronotherapy focused precoated | Prednisone | Rheumatoid arthritis | Lodotra |
| Geomatrix™ | Multilayered tablet | Verapamil | Calcium channel blocker | |
| OROS® | Osmotic | Methylphenidate | Anti-psychotic | Concerta® |
| Port® | Osmotic | Food Nutrition | Supplement of diet | |
| Pulsincap® | Rupturable system | Metronidazole | Antihelminthic | |
| Pulsincap® | Rupturable system | Dofetilide | Hypertension | |
| PULSYS ™ | Multiple pellets with different release profiles | Amoxicillin | Antibiotic | Moxtag™ |
| Three dimensional printing® | Externally regulated system | Diclofenac sodium. | Inflammation | Theirform® |
| TIMERx® | Erodible/soluble barrier coating ER tablets | Oxymorphone | Pain management | OPANA® |

**CONCLUSION**

The circadian disorders generally require Chrono pharmaco therapy, which can be easily accomplished by pulsatile drug delivery system in a very organized manner. With the advent of pulsatile drug delivery, one can remain assured of accomplishment of the goal for safe and effective 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. Today's drug delivery technologies enable the incorporation of drug molecules into new delivery systems, thus providing numerous therapeutic and commercial advantages. The overall success of Chronotherapeutics depends on the successful integration of knowledge from future advances in development timing, system biology and nanotechnology. Since the timing of drug administration in disease therapy has the remarkable impact upon treatment success, Chronotherapeutics remains a crucial and potential area for continuing research.

**CONFLICT OF INTERESTS**

Declared None

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