

## Chronotropic Systems; an Emerging Trend in Drug Delivery for Pulsed Release in Chronopharmacotherapy

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### ABSTRACT

Advances in chronobiology, chronopharmacology and requirement of an appropriate technology to deliver the drug at specific time and site resulted into novel type of drug delivery systems, 'chronotropic or pulsatile drug delivery systems'. The principle rationale behind designing these delivery systems is to release the drug at desired time as per the pathophysiological need of disease, resulting in improved patient therapeutic efficacy and compliance. As the name suggests, these systems are meant for chronopharmacotherapy, treatment of those diseases that are caused due to circadian changes in body. These systems are developed when zero order drug release is not desired. Pulsatile drug delivery systems are designed to release certain amount of drug within a short period of time, immediately after a predetermined lag time. Diseases wherein chronotropic systems are promising include asthma, peptic-ulcer, cardiovascular diseases, arthritis, attention-deficit syndrome in children and hypercholesterolemia etc. Various approaches like capsular systems, systems with different type of barrier coatings, stimuli sensitive Pulsatile systems and externally regulated systems are summarized in this article. The current article focuses on diseases requiring chronotropic systems, approaches to design them, recent technologies for chronotherapy and currently available marketed formulations.

**Keywords:** Chronopharmacotherapy, circadian rhythm, Pulsatile drug delivery system, capsular systems, erodible and rupturable systems.

### INTRODUCTION

Daily rhythms in plants and animals have been observed since early times. In fourth century BC, Alexander the Great's Scribe Androsthenes noted that the leaves of certain trees opened during day and closed at night, showing a clear rhythmicity. [1] Circadian rhythms of behavior in mammals are known to be robust and precise. The efficacy and toxicity of many drugs vary depending upon the relationship between the dosing schedule and the 24 hour rhythms of biochemical, physiological and behavioral processes. Also several drugs cause alterations to 24 hours rhythms leading to illness and altered homeostatic regulation. The alteration of biological rhythm is a new concept of adverse effects, which can be minimized by optimizing the dosing schedule. [2]

Traditionally, drug delivery was meant for getting drug absorbed and absorption should be predictable from gut or site of injection. Whereas second generation drug delivery goal was to achieve perfection in continuous and constant rate delivery of bioactive agents. However living organisms are not "zero order" in their requirement or response to drugs.

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They are predictable resonating dynamic systems whom require different amounts of drug at predictably different time within circadian cycle which will maximize desired and minimize undesired drug effects.

Hence a novel drug delivery approach; chronotropic systems have been designed for the following reasons:

- i. Chronopharmacotherapy of diseases in which circadian rhythms play important role in their pathophysiology.
- ii. To avoid degradation of drugs in upper gastrointestinal tract (proteins and peptides)
- iii. For programmed delivery of hormones, since continuous release dosage forms may lead to disturbance in normal feedback mechanism of body as well as development of resistance may also take place.
- iv. For drugs which develop biological tolerance/(nitroglycerines), undergo extensive first pass metabolism and that are targeted to specific site of gastrointestinal tract e.g. colon. [3]

Chronotropic systems are designed over the concept of chronopharmaceutics in which there is a specificity in delivering higher amount of drug in a burst at circadian timings correlated with specific pathological disorder to achieve maximum drug effect. In these systems there is a

transient release of certain amount of drug within a short period of time immediately after a predetermined off-release period.

**Chronopharmaceutics; definition and concept**

Chronopharmaceutics consist of two words, “chronobiology” and “pharmaceutics”. Chronobiology is the study of biological rhythms and their mechanism. There are three types of mechanical rhythms in our body:

- a) Circadian rhythms:-The term “circadian” was coined by Franz Halberg from Latin words “circa” meaning “about” and “dies” meaning “day”. Oscillations in our body that are completed in 24 hours are termed as circadian rhythms.
- b) Ultradian rhythms: - Oscillations that are completed in a shorter duration of less than 24 hours are termed as ultradian rhythms (more than one cycle per day).
- c) Infradian rhythms: Oscillations that are completed in more than 24 hours are termed as infradian rhythms (less than one cycle per day).

**Diseases of known pathogenesis associated with oscillatory changes of body**

Before designing a chronotropic or pulsatile drug delivery system, understanding of a disease and role of circadian rhythm in its pathophysiology is required. Diseases that are currently targeted by chronotropic systems are those for which there is enough scientific background to justify their need for chronotropic systems as compared to conventional drug delivery systems. Particular rhythms in the onset and extent of symptoms were observed in diseases such as bronchial asthma, myocardial infarction, angina pectoris, rheumatic disease, ulcer, diabetes, attention deficit syndrome, hypercholesteremia and hypertension. Table 1 enumerates various diseases and their chronological behavior.

In case of asthma, aggravation of attacks occur in early morning or after midnight, the reason is low lung function is promoted by circadian changes at that time (due to release of nor epinephrine and epinephrine). Also in case of cardiovascular diseases several functions of heart (blood pressure, heart rate, stroke volume, cardiac output, and blood flow) get affected according to circadian changes leading to angina, hypertension, myocardial infarction, stroke etc. Circadian variations of glucose and insulin in diabetes have been extensively studied. Furthermore circadian changes also contribute in lipid metabolism in patients as well as in normal subjects, leading to complication in cholesterol synthesis in patients. [4] Plasma concentration of C - reactive protein and interleukin-6 increases in rheumatic patients during morning hours due to circadian changes.

**VARIOUS APPROACHES TO DESIGN CHRONOTROPIC SYSTEMS TO ACHIEVE PULSATILE DRUG RELEASE**

Several methodologies have been developed and applied to design chronotropic systems for desired Pulsatile drug release. These methodologies can be broadly classified into 3 major categories:

- Time controlled chronotropic systems.
- Stimuli induced pulsatile drug delivery systems
- Externally regulated pulsatile drug delivery systems

**Time controlled chronotropic systems**

In these type of systems, there is a burst release of drug within a short period of time immediately after a predetermined off release period. These systems can be

further classified into different subtypes according to methodologies applied to design them:

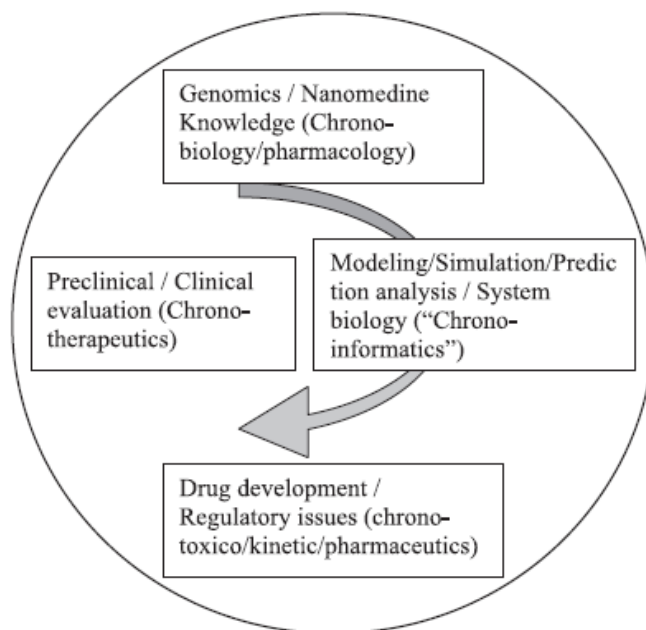


Fig.1: Key steps in designing of chronotropic systems.

Table 1: Target Diseases In Chronotherapy

Disease	Chronological behavior and symptoms	Drugs used
Asthma	Precipitation of attacks after midnight or at early morning hours.	Beta-agonists, antihistaminic
Cardiovascular diseases	BP lowers during sleep cycle but rises steeply at early morning hours.	Nitroglycerin, calcium channel blockers
Arthritis	Increased conc. of c-reactive protein and interleukin-6 in blood. Pain in early morning compared to day time.	NSAIDs, Glucocorticoids
Diabetes mellitus	Increase in blood sugar level after meal.	Sulfonylurea, insulin
Attention deficit syndrome	Increase in DOPA level in afternoon.	Methylphenidate
Hypercholesteremia	Increased cholesterol synthesis during night w.r.t day time.	HMG CoA Reductase inhibitors
Peptic ulcer	Acid secretion increases in in night as well as in afternoon.	Proton pump blockers

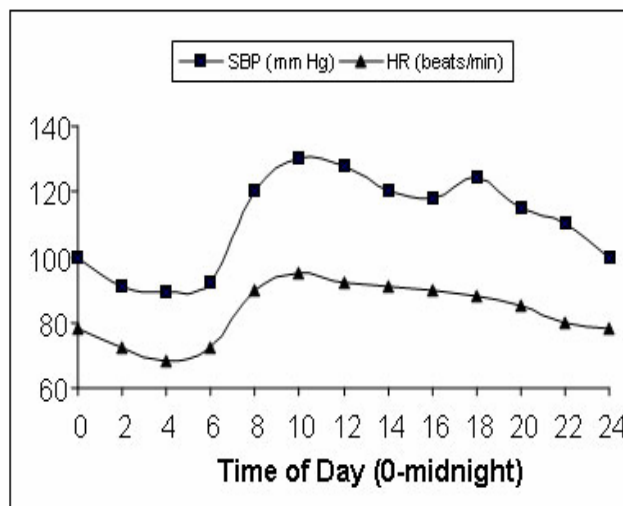


Fig. 2: Schematic diagram of circadian variation in systolic blood pressure and heart rate.

### Time controlled chronotropic systems based on capsule

Capsular systems are generally comprised of "Pulsincap system", which consists of an insoluble capsule body, swellable and degradable plugs made of approved substances such as hydrophilic polymers and lipids and bioactive molecule. The lag time is controlled by plug, which is pushed away by swelling or erosion and drug is released as a pulse from the insoluble capsule i.e. Pulsincap. A swellable hydrogel seals the drug contents into the capsule body. When this capsule body comes in contact of dissolution medium, the hydrogel plug swells and after a lag time, the plug pushes itself outside the capsule and rapidly releases the drug. The polymers generally used for plugs include hydroxyl propyl cellulose, poly vinyl acetate, polyethylene-oxide e.t.c. The swelling strength of plug decides the lag time. The dosage form comprises of a multitude of multicoated particulates. The time controlled series of pulses occur several hours of oral administration with or without immediate release. The composition and thickness of polymeric membranes determine the lag time and duration of drug release from each of multiparticulate formulations. Many of the drugs have been formulated in form of pulsincap systems for hypertension, angina, peptic ulcer etc. Gohel and Sumitra developed a system wherein weighed quantity of dicalcium phosphate was filled into the capsule body followed by drug (Diltiazem HCl). Weighed amount of the hydrophilic swellable polymers such as HPMC/guar gum was placed on top and compressed lightly using a rod to form a compact plug.<sup>[5]</sup> To simplify this technology the hydrogel plug has been replaced by an erodible tablet, which has a tight fit in the capsule to prevent the entry of fluid during the release process it erodes away from the mouth of capsule.<sup>[6]</sup>

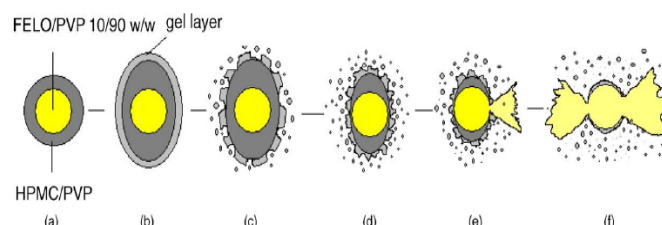
### Time controlled reservoir systems with rupturable polymer coating

These are either single unit or multiparticulate reservoir systems with outer rupturable barrier. Upon water ingress, a hydrostatic pressure develops within the system and this leads to rupturing of surrounding polymeric layer resulting drug release from the core of system. Pressure buildup required to rupture the coating can be achieved by using swelling agents, gas producing effervescent agents or osmogens. Rate of water permeation and mechanical resistance of the outer membrane are major factors affecting the lag time.

Mechanism of drug release is either diffusion or dissolution according to the nature of drug. Ueda *et al.* discovered time controlled explosion systems for water insoluble drugs in both single as well as multiple unit dosage forms.<sup>[7-10]</sup> Both types of dosage forms contain a core of drug plus osmotic agent and super disintegrants. Finally the cores are coated with a protective polymeric rupturable layer and a top water insoluble semi permeable layer, which is the rate controlling membrane for influx of water into osmotic core. Different type of release pattern can be obtained in different types of dosage forms, for instance in case of tablets, drug is released quickly after the explosion of outer membrane while in case of pellets or granules, drug is released with zero order pattern after a definite lag time because of the time variance of the explosion of the outer membrane. In each bead or granule, drug release is time controlled by the rupturing of external water insoluble membrane caused by explosive swelling effect of the swelling agents. The lag time increases with increasing coating level and higher amount of talc and

plasticizer in coating. Drug release from time controlled explosion systems was found to be complete, independent of environmental pH and drug solubility. But these systems has a drawback of failing to release drug if swelling agents fail to rupture the water insoluble coating and having limited flexibility in the release pattern and also maximum lag time of approximately four hours has been reported.

To have a better control over release pattern, water soluble polymer (mainly pH dependent) can be incorporated in insoluble polymeric membrane so that at elevated pH of small intestine, polymer begins to dissolve thus weakening of membrane can be assured after a predetermined lag time. Also by varying the coat thickness as well as proportion of soluble and insoluble material in the coating, the lag time before drug release can be prolonged with better control and reliability, with eventual disintegration of coating ensuring release of drug.<sup>[11]</sup> Diclofenac sodium pulsatile release pellets were prepared by extrusion-spheronisation technology and coated in a mini fluidized bed spray coater with swelling material as the inner coating swelling layer and ethyl cellulose aqueous dispersion as the outer coating controlled layer. The lag time for pulsed delivery of diclofenac was found to be good agreement between *in vitro* and *in vivo*.



**Fig. 3: Rupture mechanism of double wall tablets.** (a) Initial tablet, (b) gel forming on the coating layer due to the water penetration and tablet swelling (c) erosion inception of the coating layer (d) extended erosion (e) rapture of coating layer and initiation of core dissolution and (f) extended FELODIPINE release.

### Time controlled reservoir systems with soluble or eroding polymer coating

These systems are another class of reservoir type pulsatile systems with a barrier layer, which dissolves or erodes after a specific lag time followed by burst release of drug from the reservoir core. Generally in these types of systems, the lag time prior to drug release is controlled by thickness of coating layer. For instance, a chronotropic system which consists of a drug containing core layered with HPMC and a top layer of enteric coating, the lag time before drug release will be dependent upon the thickness and viscosity grade of HPMC layer. Since drug release mechanism in these types of systems is dissolution, that's why, a high degree of drug solubility relative to dose of drug is essential for rapid release of drug after the lag period. Various grades of hydroxyl propyl methyl cellulose and Eudragit (acrylate) polymers have been studied to in an attempt to deliver drugs to various sites in gastrointestinal tract due to their solubility and eroding properties. Formulations dependent on slow dissolution behavior of high viscosity polymers is described by Gazzaniga *et al.* It consists of mini tablets with therein dispersed a drug substance which is coated with a high viscosity polymer (HPMC 40000) and an outer enteric coating. The outer film protects the system from fluids in the stomach and dissolves upon entering in small intestine. HPMC layer delays the drug release for 3-4 hours when the system is transported through small intestine.<sup>[12]</sup>



Fig. 4: Expected behavior and release profile of swellable/erodible reservoir systems for oral pulsatile delivery

#### Pulsatile systems based on changed membrane permeability

These systems are designed when a sigmoidal release pattern is desired, therapeutically beneficial for timed release and colonic drug delivery. Drug release is achieved by change in permeability of polymeric coating layer in presence of certain counter ions of surrounding media, based on this Narisawa *et al.*, developed a device capable of pulse-release depending on the change in diffusion properties of Eudragit RS. [13-14] They analyzed that core of theophylline coated with Eudragit RS showed very slow release in pure water but significant increase in release rate was found when the microcapsules were immersed in an organic acid solution containing succinic acid, glutaric acid, tartaric acid, malic acid or citric acid. The reason behind that was higher hydration of film containing quaternary ammonium groups in the polymer chain, were not affected by succinic acid, suggesting that the quaternary ammonium groups of Eudragit RS are essential to produce unique drug release profile. The release profile of systems based on permeability changes depend strongly on physicochemical properties of the drug and its interaction with membrane. Therefore, with this system a pulsatile release profile may be obtained for some particular drug molecules in a specific formulation but can not be generally applied to all drugs.

#### Time controlled, low density floating pulsatile systems

As the name suggests these systems are comprised of low density floating pulsatile dosage forms, reside in stomach only and not affected by variation in gastric pH, local environment or gastric emptying rate. These dosage forms may be either single unit (floating tablets) or multiparticulates (beads, pellets, granules, microspheres) with capability of gastro-retention. These are specifically advantageous for drugs either absorbed from the stomach or requiring local delivery in stomach. Polysaccharides are widely used in oral delivery systems because of simplicity to obtain the desired drug delivery system and drug release profile, by the control of cross linking, insolubility of cross linked beads in gastric environment and broad regulatory acceptance. Badave *et al.* developed hollow calcium pectinate beads for floating pulsatile release of diclofenac sodium intended for chronotherapy. [15]

A multiparticulate floating pulsatile drug delivery system was developed using porous calcium silicate (Fluorite RE) and sodium alginate for time and site specific drug release of meloxicam for chronopharmacotherapy of rheumatoid arthritis. [16] Meloxicam was adsorbed on the Fluorite RE by fast evaporation of solvent from drug solution containing dispersed Fluorite. Drug adsorbed fluorite powder was used to prepare calcium alginate beads by ionotropic gelation method. The floating time for this system was controlled by density of beads and hydrophobic character of drug. To

overcome limitations of various approaches for imparting buoyancy hollow/porous calcium pectinate beads were prepared by simple process of acid base reaction during ionotropic cross linking. The floating beads provide two-phase release pattern with initial lag time during floating in acidic medium followed by rapid pulse release in phosphate buffer. These drug delivery systems show distinct behavior from other approaches in chronotherapy with desired low drug release in acidic medium, reduced time consumption due to single step process and also overcame the limitations of process variable caused by multiple formulation steps.

#### Stimuli induced pulsatile drug delivery system

These systems are designed on the basis of physicochemical processes of body. In other words these systems are novel drug delivery approaches meant for targeted drug delivery at specific site due to induction of certain physicochemical stimuli at target site. Biological stimuli like release of certain enzymes, hormones, antibodies, pH of the site, temperature of the site, presence of certain cells, concentration of biomolecules (glucose, neurotransmitters, inflammatory mediators) etc act as stimuli to trigger the release of drug from these type of drug delivery systems. These systems can be further classified into two sub categories:

*Chemical stimuli induced pulsatile drug delivery systems.*

*Temperature induced pulsatile drug delivery systems.*

#### Chemical stimuli induced pulsatile drug delivery systems

These systems can be described by certain examples of chemical stimuli like:

#### Glucose-responsive insulin release devices

In Diabetes-mellitus Type-1, it was depicted earlier that there is an increase in blood glucose concentration rhythmically and several systems were developed which responded to changes in glucose concentration. One such stimuli induced system includes pH sensitive hydrogel containing glucose oxidase enzyme immobilized in hydrogel. As the blood concentration of glucose rises, glucose-oxidase converts glucose into gluconic acid, which changes the pH of system. Due to change in pH, swelling of polymer takes place and these results into insulin release. Insulin decreases the blood glucose level and consequently the gluconic acid level also declines and system turns to deswelling and hence decreasing the insulin release. Examples of pH sensitive polymers include n-dimethyl amino ethyl methacrylate, chitosan, polyol etc.

Okan *et al.* developed the system based on the fact that boronic acid moiety forms reversible bonds with polyol compounds including glucose. They used water soluble copolymers containing phenyl boronic acid side chains which showed formation of a reversible complex gels with polyol compounds such as PVA. Such complexes are dissociated after the addition of glucose in a concentration dependent manner.

#### Inflammation induced pulsatile drug delivery systems

Inflammation caused by any physical or chemical stress (injury, fracture etc) acts as a stimulus due to hydroxyl radicals produced from inflammation responsive cells. Yui *et al.* designed and developed inflammation responsive pulsatile drug delivery system which responded to hydroxyl radicals and degraded in a limited manner. They utilized hyaluronic acid which is specifically hydrolyzed by hyaluronidase or free radicals present at inflammatory site abundantly w. r. t normal tissue. Hence it became possible to treat patient with inflammatory diseases like rheumatoid arthritis, using

NSAIDS incorporated into hyaluronic acid gels as a new implantable drug delivery system.

#### **Targeted delivery by pulsatile release intelligent gels responding to antibody concentration**

In many infectious diseases, microbes become resistant towards antibiotic concentration due to development of tolerance. Therefore in order to kill all microbes, that are multiplying as well as in dormant phase, a pulsatile release of antibiotic is desired. Novel kinds of gels have been developed that respond to change in antibiotic concentration to alter their swelling/deswelling characteristics. Utilizing the difference in association constants between polymerized antibody and naturally derived antibody towards specific antigens reversible gel swelling/deswelling and drug permeation changes occur.

#### **pH sensitive pulsatile release chronotropic systems**

It is a widely accepted and versatile approach to design chronotropic systems to attain specified lag time prior to drug release by using pH dependent polymers. These can be single unit or multiparticulate dosage forms with reliable and predictable drug release profile. These type of systems possess the advantage of fact there exists different pH environment at different parts of gastrointestinal tract. Hence by employing pH dependent polymers targeting at specific site of gastrointestinal tract is possible as well as a desired lag time can be achieved due to dependency of polymer solubility only at a particular pH of gastrointestinal tract. Examples of pH dependent polymers include copolymers of methacrylic acid (various grades of Eudragit), phthalates, carboxy methyl cellulose etc. these polymers are utilized for enteric coating to protect the drug from degradation in upper G. I. T and attain drug release at specific part of intestine (according to solubility of polymer at particular pH and specific site of intestine) after a predetermined lag time. A number of chronotropic systems have been developed and marketed for chronotherapy utilizing pH dependent polymers for asthma, angina, rheumatoid arthritis, cancer, diabetes, ulcer etc. Akhgari *et al* studied on the optimum ratio of eudragit100 and Eudragit S1000 for colonic delivery of indomethacin pellets for chronotherapy of rheumatoid arthritis.<sup>[17]</sup> In a study Gupta *et al* attempted to exploit various grades of Eudragit soluble at pH more than 7 to achieve colonic delivery of 5-aminosalicylic acid for treatment of irritable bowel syndrome.<sup>[18]</sup> Also colon targeted chronotropic systems of theophylline, diltiazem, verapamil, budesonide, nitroglycerine etc have been formulated to treat asthma, angina and hypertension.

#### **Enzyme catalyzed pulsatile chronotropic systems**

These systems are generally designed for colonic delivery of drug where release rate is dependent upon the catalysis of polymeric membrane by enzymes secreted by colonic microflora. Hence it enables the more specific targeting, independent of pH variations along the gastrointestinal tract. Many natural polysaccharides such as chondroitin sulphate, pectin, dextran, guar gum etc have been investigated for their potential in designing colon specific drug delivery. The use of polysaccharides for coating purposes has been tried with limited success. Most of the non starch polysaccharides suffer from the drawback of lacking good film forming properties. Also they tend to swell in gastrointestinal tract and become porous resulting in early release of drug. Chronotherapy of rheumatoid arthritis has been tried by utilizing these polymers to deliver NSAIDS in colon after a

lag time of 4-6 hours to relieve pain in early morning. Also pulsatile delivery of 5-aminosalicylic acid has been attempted in case of irritable bowel syndrome.

#### **Temperature induced pulsatile drug delivery systems**

Among various types of cells inside the body, not all of them are at same physiological temperature. Certain cells possess somewhat different temperature (either higher or lower) with respect to other cells like tumor cells, in which cellular temperature is raised due to their higher metabolic rate. For targeting tumors, a pulsatile drug delivery system can be designed by utilizing thermoresponsive hydrogel system. As the name suggests, these polymers undergo swelling/deswelling phenomena in response to temperature change (at different metabolic rates of tumour cells) which modulates drug release from these systems. YH Bae. *et al* developed indomethacin pulsatile drug delivery system in temperature range of 20°C-30°C by using reversible swelling properties of copolymers of N-isopropyl acrylamide and butyrylacrylamide. Kataoka *et al* developed the thermosensitive polymeric micelles as drug carrier to treat cancer.

#### **Externally regulated pulsatile drug delivery systems**

These systems are modulated to release drug by some external stimuli like magnetic field, ultrasound, electrical effect and irradiation. When these external forces are applied on the system, conductors present in the delivery system get sensitized to trigger the release of drug from the dosage form and as the external stimuli is removed, drug release ceases, demonstrating the pulsatile release of drug from the system. Due to advances in technology, a number of externally regulated systems have been developed for targeted delivery of drug at specified time and desired site of body. Examples of such systems include magnetic beads in an implant; photochemically controlled delivery systems prepared by interfacial polymerization of polyamide microcapsules.

### **TYPES OF DOSAGE FORMS THAT CAN BE DESIGNED**

#### **Compression coated/press coated tablets**

These are timed release formulations, simple to manufacture, comprised of an inner core that contains an active pharmaceutical ingredient and excipients surrounded by an outer layer that dissolves or disintegrates slowly to produce the lag time. The core is placed between two layers of polymer and directly compressed by flat punches of tablet machine. Surrounding polymeric layers protect the drug from release before the desired lag time, hence effective delivery in chronotherapy as it allows the drug release at the point in circadian cycle when clinical signs develop and increase. Drugs that treat cardiovascular disease (nifedipine, nitrendipine, amlodipine, diltiazem etc) and asthma (theophylline, budesonide) had been attempted to formulate such dosage forms. Swada *et al.* 2003 prepared timed release compression coated tablets of nifedipine for chronotherapy of angina and compared its *in vitro-in vivo* release profile with sustained release formulation.<sup>[19]</sup>

#### **Core in cup tablets**

It is a novel oral pulsatile release drug delivery system based on a core-in-cup dry coated tablet, where the core tablet surrounded on the bottom and circumference wall with inactive material. The system consists of three different parts, a core tablet, containing active ingredient, an impermeable outer shell and a top cover layer-barrier of a soluble polymer. The impermeable coating cup consisted of cellulose acetate

propionate and the top cover layer of hydrophilic swellable materials such as polyethylene oxide, sodium alginate or sodium carboxy methyl cellulose. The system releases the drug after a certain lag time generally due to the erosion of top cover layer. The quantity of material, its characteristics (viscosity, swelling, gel layer thickness) and the drug solubility was found to modify lag time and drug release.<sup>[20]</sup> The lag time increases when quantity of top layer increases, whereas drug release decreases.

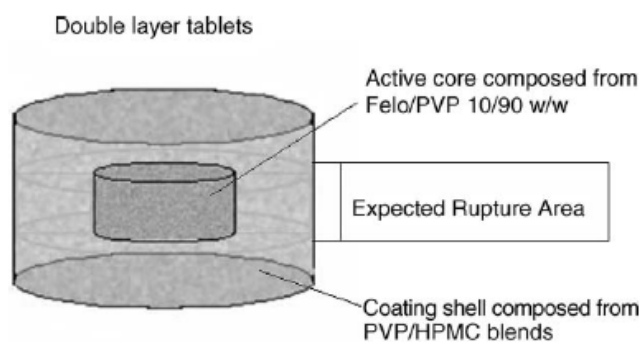


Fig. 5: Design of the press coated tablet composed of an active FELODIPINE/PVP core and an inactive PVP/HPMC coating layer.

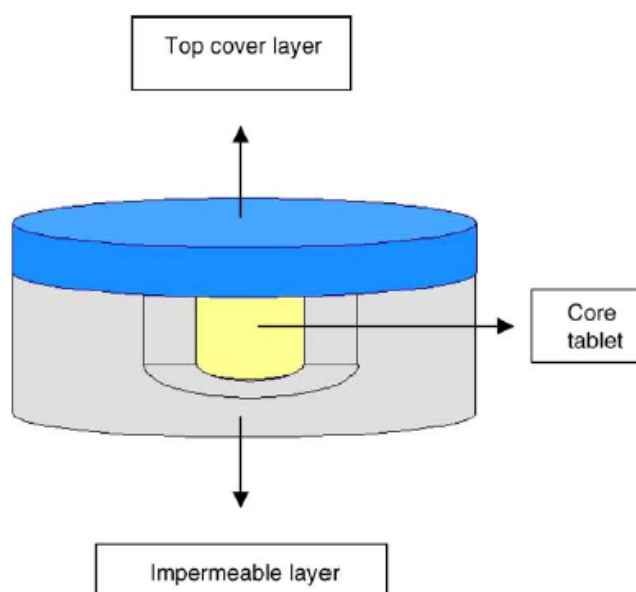


Fig. 6: Schematic representation of "core in cup tablet" as a pulsatile drug delivery system.

### Pulsincap systems

As discussed previously that these are the well designed pulsatile release drug delivery systems capable of releasing drug at a pre determined time. Drug formulation is contained within the insoluble capsule body which is sealed by means of a hydrogel plug. On oral administration the water soluble capsule cap dissolves in the gastric juices and hydrogel plug swells. At a controlled and predetermined time point after the ingestion, the swollen plug is ejected from the pulsincap dosage form after which the encapsulated dosage formulation is then released.<sup>[21]</sup> To simplify this technology, the hydrogel plug has been replaced by an erodible tablet, which has a tight fit in capsule to prevent the entry of fluid. During the release process it erodes away from the mouth of capsule. The effect of various parameters such as type and weight of swellable polymer, type of hydrophilic polymers used in

erodible tablet formulation and erodible tablet weight was investigated in order to characterize the lag time and drug release profiles.

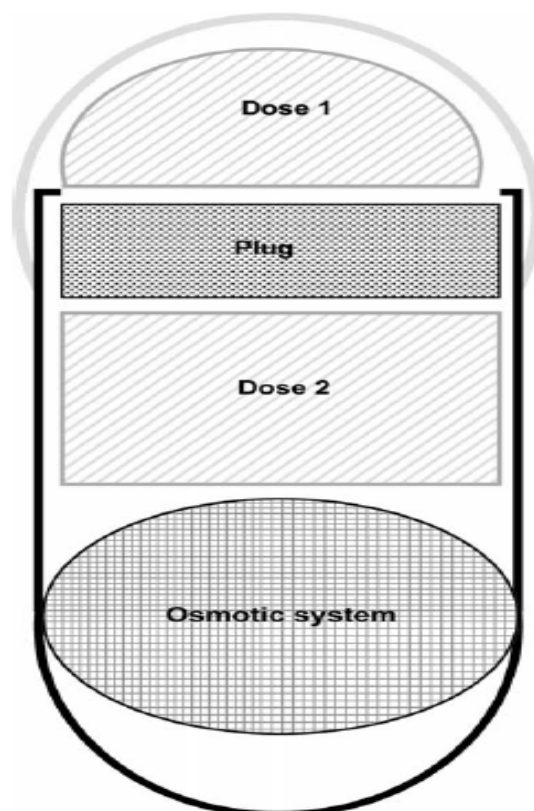


Fig. 7: The pulsatile capsule is designed for two drug doses. first is placed into the capsule cap while the second dose is released from an insoluble capsule body.lag time is determined by an osmotic system which presses an insoluble plug out of the capsule body.

### Double coated hard gelatin capsules and double coated tablets

These are time controlled rupturable pulsatile drug delivery systems either in form of hard gelatin capsules tablets. The capsules are filled with active pharmaceutical ingredient either for single pulse or multi-pulse release (in form of multiparticulates) and coated with a swelling layer followed by an external water insoluble semipermeable polymeric coating. Upon water ingress the swelling layer swells to attain a threshold hydrodynamic pressure required to rupture the outer coating and allowing the release of contents in surrounding medium. The time required by swelling layer to rupture outer coating serves the purpose of desired lag time required in chrono therapy of disease.<sup>[22]</sup>

The tablets are manufactured and coated on the same principle as that of double coated gelatin capsules.

### Pulsatile release multiparticulate systems

These systems have been developed on the basis of various approaches of designing pulsatile drug delivery system discussed earlier( like time controlled, stimuli induced or externally regulated pulsatile drug delivery systems).these can be developed in various types of dosage forms like:

- i. Pellets
- ii. Granules
- iii. Microspheres
- iv. Beads
- v. Nanoparticles
- vi. Microsponges

In recent pharmaceutical applications involving pulsatile drug delivery, multiparticulate dosage forms are gaining much favour over single unit dosage forms. The potential benefits include increased bioavailability, predictable, reproducible, and generally short gastric residence time; no risk of dose dumping; reduced risk of local irritation; and flexibility to blend pellets with different compositions or release patterns. Because of their smaller particle size, these systems are capable of passing through gastrointestinal tract easily, leading to less inter- and intra-subject variability. A no. of multiparticulate pulsatile drug delivery systems have been developed for chronotherapy. For instance, colonic delivery of theophylline in form of microspheres and coated pellets for nocturnal asthma<sup>[23]</sup>, formulation of indomethacin, ibuprofen, flurbiprofen, meloxicam, aceclofenac, diclofenac pellets and microspheres for chronotherapy of rheumatoid arthritis and floating beads of alginates encapsulating the active drug component in core, have been attempted to deliver many of the drugs which are absorbed in upper gastrointestinal tract. Numerous advanced technologies have been developed in designing of pulsatile release multiparticulate dosage forms and many of them are FDA approved and being marketed.

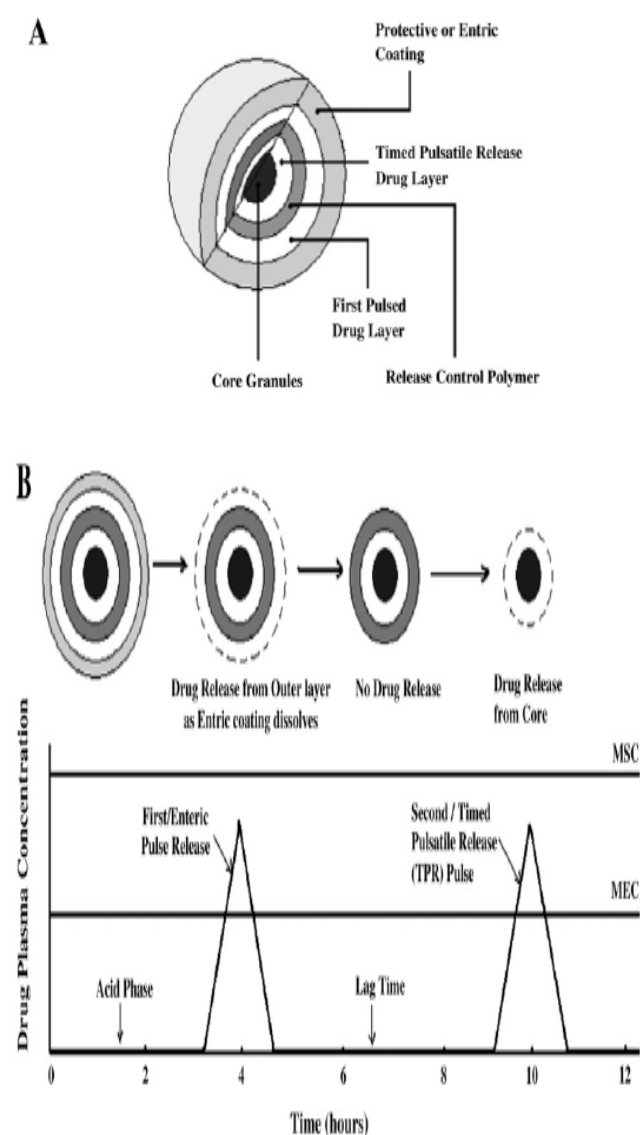


Fig. 8: Hypothetical design and plasma drug profile of a multiparticulate pulsatile system. (A) Design of a pellet with multiple coatings, and (B) Predicted bi-modal plasma concentration profile.

### Chronomodulating infusion pumps

Externally and internally controlled systems across a range of technologies including pre-programmed systems, as well as systems that are sensitive to modulated enzymatic or hydrolytic degradation, pH, magnetic fields, ultrasound, electric fields, temperature, light and mechanical stimulation have been reviewed in detail elsewhere. To our knowledge infusion pumps on the market that have been referred to as chronomodulating for drug delivery application include the Melodie, programmable Synchromed, Panomat V5 infusion, and the Rhythmic pumps.<sup>[1]</sup> The portable pumps are usually characterized by a light weight (300-500 g) for easy portability and precision in drug delivery. For example portable programmable multi-channel pumps allowed demonstration of the clinical relevance of the chronotherapy principle in a sufficiently large patient population. Specifically, a clinical phase III trial involving several patients with metastatic gastrointestinal malignancies compared a flat versus the chronomodulated three-drug regimen, and demonstrated large, simultaneous improvements in both tolerability and response rates in patients with metastatic colorectal cancer receiving chronotherapy. In case of insulin therapy, implantable infusion pumps 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 the intraperitoneal route. The insulin reservoir is refilled once a month or every 3 months at a physician's office by inserting a needle through the skin into the pump (a local anesthetic is first used). Doses adjustments are made by the patient (within ranges established by the physician) using radiotelemetry and an electronic device that is held over the pump. Their advantages include the fact that the peritoneum provides a large, well-vascularized surface area, and absorption is faster by this route than after subcutaneous injection (better insulin gradient), improved glyemic control and a reduction in the frequency of hypoglycemic episodes. Possible drawbacks of this approach include eventual formation of fibrous tissue pocket and local skin erosion. Catheter blockade which can reduce insulin delivery, are the most common problems with implantable pumps. However, these pumps have been effectively used in the chronotherapy of several diseases such as cancer and diabetes.

### Controlled-release microchip

An alternative method to achieve pulsatile or chronopharmaceutical drug release involves using microfabrication technology.<sup>[1]</sup> Santini *et al.* reported a solid-state silicon microchip that can provide controlled release of single or multiple chemical substances on demand.<sup>[24]</sup> The release mechanism was based on the electrochemical dissolution of thin anode membranes covering microreservoirs filled with chemicals in solid, liquid or gel form. Initially the authors conducted proof-of-principle release studies with a prototype microchip using gold and saline solution as a model electrode material and release medium, and demonstrated controlled, pulsatile release of poly (L-lactic acid) and had poly (D, L-lactico- glycolic acid) membranes were fabricated that released four pulses of radio-labelled dextran, human growth hormone or heparin in vitro. This technology has the potential to be used in the

design of chronotropic drug delivery systems with a better control over drug release kinetic in order to match biological requirement over a versatile period of time.

### **RECENT ADVANCES IN PULSATILE DRUG DELIVERY**

Chronotropic systems are now emerging as novel trend in drug delivery for chronotherapy due to advanced technologies and desired therapeutic application, among these, multiparticulate systems (beads, pellets, microspheres etc) possess various advantages over single unit various pulsatile technologies have been developed on the basis of approaches discussed previously. These include:

#### **OROS**

OROS technology uses an osmotic mechanism to provide pre-programmed, controlled drug delivery to the gastrointestinal tract. The dosage form comprises a wall that defines a compartment. The active drug is housed in a reservoir, surrounded by a semi-permeable membrane/wall (e.g. cellulose esters, cellulose ethers and cellulose ester-ethers) and formulated into a tablet. The tablet is divided into two layers, an active drug layer and a layer of osmotically active agents (e.g. poly ethylene oxide). Water from the gastrointestinal tract diffuses through the membrane at a controlled rate into the tablet core, causing the drug to be released in solution or suspension at a predetermined rate. This creates a 'pump' effect that pushes the active drug through a hole in the tablet. This technology, especially the OROS, Delayed Push– Pull System, also known as controlled onset extended release (COER) was used to design Covera-, a novel anti-hypertensive product. It actually enabled delayed, overnight release of verapamil to prevent the potentially dangerous surge in BP that can occur in the early morning.<sup>[25]</sup>

#### **CODOS**

The Chronotherapeutic Oral Drug Absorption System (CODAS) is a multiparticulate system which is designed for bedtime drug dosing, incorporating a 4-5 h delay in drug delivery. This delay is introduced by the level of non-enteric release-controlling polymer applied to drug loaded beads. The release controlling polymer is a combination of water soluble and water insoluble polymers. As water from the gastrointestinal tract comes into contact with the polymer coated beads, the water soluble polymer slowly 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. The rate of release is essentially independent of pH, posture and food. The nighttime dosing regimen of (CODAS-Verapamil) was not associated with excessive BP reductions during the sleeping hours. The CODAS-verapamil extended release capsules (Verelan PM) as chronotropic drug delivery systems actually provided enhanced BP reduction during the morning period when compared with other time intervals of the 24-h dosing period.

#### **CONTIN**

In this technology, 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) which may be varied. This technology has concretely enabled the development of tablet forms of sustained-release aminophylline, theophylline, morphine, and other drugs. Research suggested that evening administration of Uniphyl (anhydrous theophylline) tablets represented a rational dosing schedule for patients with asthma who often exhibit increased bronchoconstriction in the morning. Patients demonstrated improved pulmonary function in the morning compared with use of twice-daily theophylline when once-daily Uniphyl was administered in the evening. Thus, evening administration of once-daily theophylline may block the morning dip in lung function commonly seen. CONTIN technology provides for closer control over the amount of drug released to the bloodstream, and benefits patients in terms of reducing the number of doses they need to take every day, providing more effective control of disease (particularly at night),

#### **TIMER<sub>x</sub>**

The TIMER<sub>x</sub> technology (hydrophilic system) combines primarily xanthan and locust bean gums mixed with dextrose. The physical interaction between these components works to form a strong, binding gel in the presence of water. Drug release is controlled by the rate of water penetration from the gastrointestinal tract into the TIMER<sub>x</sub> gum matrix, which expands to form a gel and subsequently releases the active drug substance. This system can precisely control the release of the active drug substance in a tablet by varying the proportion of the gums, together with the third component, the tablet coating and the tablet manufacturing process.

#### **DIFFUCAPS**

In the DIFFUCAPS technology, a unit dosage form, such as a capsule for delivering drugs into the body in a circadian release fashion, comprises of one or more populations of drug-containing particles (beads, pellets, granules, etc.). Each bead population exhibits a pre-designed rapid or sustained release profile with or without a predetermined lag time of 3-5 h. The active core of the dosage form may comprise an inert particle or an acidic or alkaline buffer crystal (e.g. cellulose ethers), which is coated with an active ingredient - containing film-forming formulation and preferably a water-soluble film forming composition (e.g. hydroxyl propyl methyl cellulose, poly vinyl pyrrolidone) to form a water-soluble/dispersible particle. The active core may be prepared by granulating and milling and/or by extrusion and spheronization of a polymer composition containing the API. Such a chronotropic drug delivery system is designed to provide a plasma concentration–time profile, which varies according to physiological need during the day, i.e. mimicking the circadian rhythm and severity/manifestation of a cardiovascular disease, predicted based on pharmacokinetic and pharmacodynamic considerations and in vitro/in vivo correlations. This technology has been used to formulate the first and recently FDA approved propranolol-containing chronotropic system (InnopranR XL) for the management of hypertension

#### **CEFORM**

The CEFORM technology allows the production of uniformly sized and shaped microspheres of pharmaceutical compounds. This chronotropic drug delivery system approach is based on "melt-spinning", which means subjecting of biodegradable polymer/bioactive agents combinations to the combination of temperature, thermal gradients, mechanical forces, flow, and flow rates during



processing. The microspheres obtained are almost perfectly spherical, having a diameter that is typically 150-180  $\mu\text{m}$ , and allow for high drug content. The microspheres can be used in a wide variety of dosage forms, including tablets, capsules, suspensions, effervescent tablets, and sachets. The microspheres may be coated for controlled release either with an enteric coating or combined into a fast/slow release combination. This technology has been actually used to develop Cardizem LA, 1-day diltiazem formulation as chronotropic systems.

### PULSYS

It consists of three components: one immediate release and two delayed release by using soluble and insoluble coating materials. Moxatag, tablet of amoxicillin have been formulated for infections, which is more efficient in killing of bacteria exposed to antibiotics in front loaded, sequential bursts, hence reduces the duration of therapy.

### THREE DIMENSIONAL PRINTING

Three dimensional printing (3DP) is a novel technique used in the fabrication of complex oral dosage delivery pharmaceuticals based on solid free form fabrication methods. It is possible to engineer devices with complicated internal geometries, varying densities, diffusivities, and chemicals. Different Types of complex oral drug delivery devices have been fabricated using the 3DP process: immediate-extended release tablets, pulse release, break away tablets, and dual pulsatory tablets. The enteric dual pulsatory tablets were constructed of one continuous enteric excipient phase into which diclofenac sodium was printed into two separated areas. These samples showed two pulses of release during in vitro with a lag time between pulses of about 4 h. This technology is the basis of the Their Form technology. The latter is a micro-fabrication process that works in a manner very similar to an "ink-jet" printer. It is a fully integrated computer-aided development and manufacturing process. Products may be designed on a computer screen as three-dimensional models before actual implementation of their preparation process. This versatile technology may found potential application in chronopharmaceutics in the future.

### PULSINCAP SYSTEMS

These are the well designed pulsatile release drug delivery systems capable of releasing drug at a pre determined time. Drug formulation is contained within the insoluble capsule body which is sealed by means of a hydrogel plug. On oral administration the water soluble capsule cap dissolves in the gastric juices and hydrogel plug swells. At a controlled and predetermined time point after the ingestion, the swollen plug is ejected from the pulsincap dosage form after which the encapsulated dosage formulation is then released. To simplify this technology, the hydrogel plug has been replaced by an erodible tablet, which has a tight fit in capsule to prevent the entry of fluid. During the release process it erodes away from the mouth of capsule. The effect of various parameters such as type and weight of swellable polymer, type of hydrophilic polymers used in erodible tablet formulation and erodible tablet weight was investigated in order to characterize the lag time and drug release profiles.

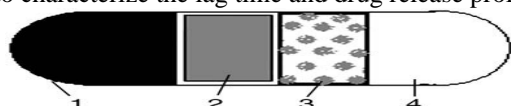


Fig. 9: Capsule assembly containing (a) swelling polymer, (2) core tablet, (3) erodible tablet and (4) soluble cap.

Table 2: Examples of chronotropic drug delivery systems available in market.

FDA-Approve-al Date	API	Proprietary name; Dosage form	Proprietary Chronopharmaceutical Technology	Indications/rationale for chronotherapy
Sept. 01, 1982	Theophylline	Uniphyll; extended release tablets	CONTIN	Asthma/increased bronchoconstriction
Oct. 15, 1986	Famotidine	Pepcid; tablets	Physico-chemical modification of API	Ulcer/increased gastric acid secretion in evening
Dec. 23, 1991	Simvastatin	Zocor; Tablets	Physico-chemical modification of API	Hypercholesterolemia
Feb. 26, 1996	Verapamil HCl	Covera-; extended release tablets	OROS	Hypertension/increased BP in early morning
Nov. 25, 1998	Verapamil HCl	Verelan; extended release capsules	CODAS	Hypertension
Feb. 06, 2003	Diltiazem HCl Verapamil HCl	Cardizem; extended release tablets	CEFORM	Hypertension
Mar. 12, 2003	Propranolol HCl, Verapamil HCl	Innopran-XL extended release capsules	DIFFUCAPS	Hypertension

### CONCLUSION

Both experimental and theoretical backgrounds, and market constraints demonstrate the clinical relevance of chronopharmaceutics, hence chronotropic systems are an emerging approach to drug delivery. Chronopharmaceutics will certainly improve patient outcome and optimize disease management in the future. The major drawbacks of existing oral chronotropic systems are their dependence human action to trigger the drug release. An ideal chronotropic system should be self regulating, taken any time and should take environmental factors in account (e.g. awake– sleep, light–dark, activity–rest status). For example, the human body is comprised of molecules, hence the availability of molecular nanotechnology that facilitate self-regulation of chronotropic systems based on body immune system and disease state will permit dramatic progress in human medical services. Moreover, the circadian clock of the suprachiasmatic nucleus (SCN) is thought to drive daily rhythms of behavior by secreting factors that act locally within the hypothalamus. Epidermal growth factor receptors signaling have been implicated in the daily control of locomotor activity, and neural circuit in the hypothalamus that likely mediates the regulation of behavior both by the SCN and the retina have been identified. Clearly, mammals possess a retinally based light-detection system that has component (e.g. melanopsin, cryptochromes) that may be potential target for efficient chronopharmaceutical drug development. The overall success of chronopharmaceutics will depend on the successful integration of knowledge from future advances in development timing, system biology and nanomedicine. The selection of the appropriate chronopharmaceutical technology should take into considerations the application range (e.g. targeted drugs of different physico-chemical

properties), the ease of manufacturing, the cost-effectiveness, and the flexibility in the pharmacokinetic profile. Pulsatile drug delivery systems are smart and efficient dosage forms satisfying needs of patients and offering interesting options for intelligent life cycle management. But due to lack of manufacturing reproducibility, large process variables and multiple formulation steps, these are still in limited no in market. But in near future due to more advancement of technology, these hurdles will be overcome and a number of patients will be greatly benefited by these systems.

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