

CHRONOTHERAPY: A NOVEL DRUG DELIVERY SYSTEM

Dubal Ashwini*, Karigar Asif, Ramana MV, Patel Mitul, Desai Omkar
Maratha Mandal's College of Pharmacy, Belgaum, Karnataka, India

Received on: 09/09/11 Revised on: 10/10/11 Accepted on: 20/11/11

*Corresponding author

Dubal Ashwini, M. Pharm II year, Email: ashwinidubal@ymail.com

ABSTRACT

Recent advances in chronopharmacology and requirement of an appropriate technology to deliver the drug at specific time and site led to the development of novel type of drug delivery systems as "chronotropic or Pulsatile drug delivery systems". Rationale behind designing these drug delivery systems is to release the drug at desired time (pathophysiological need of disease), which results into improved therapeutic efficacy and patient-compliance. These systems are meant for treatment of those diseases that are caused due to circadian changes in body like asthma, peptic ulcer, cardiovascular diseases, arthritis and when zero order drug release is not desired. These drug delivery systems are designed to release the drug within a short period of time, immediately after a predetermined lag time. The current article focuses on diseases requiring chronotropic systems and their chronological behavior, various approaches like time controlled chronotropic systems, stimuli induced pulsatile drug delivery systems, externally regulated pulsatile drug delivery systems to design them, recent technologies for chronotherapy and currently available marketed formulations.

KEY WORDS: Chronotherapy, circadian rhythm, pulsatile drug delivery system, time controlled chronotropic systems, stimuli induced pulsatile drug delivery systems, externally regulated pulsatile drug delivery systems.

INTRODUCTION

By definition, colonic delivery refers to targeted delivery of drugs into the lower GI tract, which occurs primarily in the large intestine (i.e. colon). The site-specific delivery of drugs to lower parts of the GI tract is advantageous for localized treatment of several colonic diseases, mainly inflammatory bowel diseases (Crohn's disease and ulcerative colitis), irritable bowel syndrome, and colon cancer¹⁻⁴. Other potential applications of colonic delivery include chronotherapy⁵ and treatment of nicotine addiction⁶.

Formulations for colonic delivery are also suitable for delivery of drugs which are polar and/ or susceptible to chemical and enzymatic degradation in the upper GI tract, in particular, therapeutic proteins and peptides⁷⁻⁹. Proteins and peptides such as insulin, calcitonin and vasopressin may be delivered systemically via colonic absorption. Other examples include novel peptides such as cytokine inhibitors and antibiotics (e.g., nisin), which are useful in the treatment of inflammatory bowel diseases and GI infections, respectively. Apart from protecting these labile molecules, colon also offers an opportunistic site for oral delivery of vaccines because it is rich in lymphoid tissue. Therefore, the uptake of antigens through the colonic mucosa may lead to rapid and local production of antibodies¹⁰.

Daily rhythms in plants and animals have been observed since early times. In fourth century BC, Alexander the Great's Scribe Androstenes noted that the leaves of certain trees opened during day and closed at night, showing a clear rhythmicity¹¹. 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 schedule¹².

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:

- Chonopharmacotherapy of diseases in which circadian rhythms play important role in their pathophysiology.
- To avoid degradation of drugs in upper gastrointestinal tract (proteins and peptides).
- 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.
- For drugs which develop biological tolerance/ (nitroglycerines), undergoes extensive first pass metabolism and that are targeted to specific site of gastrointestinal tract e.g. colon¹³.

Chronotropic system 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.

Circadian time structure

Circadian rhythms are controlled by an inherited master clock network composed of the paired suprachiasmatic nuclei (SCN) that are situated in the hypothalamus and the pineal gland¹⁴. The rhythmic activities of specific, so called, clock genes, like *per1*, *per2*, *per3*, *bmal*, *clock*, and *CRY*, among others, and their gene products, plus the cyclic (nocturnal) secretion of melatonin from the pineal gland comprise the central timekeeping mechanism. This master clock network orchestrates the period and phase of the multitude of subservient peripheral circadian clocks located in cells, tissues, and organ-systems. The end effect is a rather exquisite temporal organization of biological processes and functions. The daily changes in light intensities are thought to be the major environmental cue involved in circadian entrainment. Light- signals are perceived by photoreceptor cells in the retina and transmitted to neurons of the SCN via the retinohypothalamic tract. A great deal of research shows that the inherited period of the human pacemaker clock is not precisely 24 h. In fact, in most people, it is somewhat longer, closer to 25 h. Environmental time cues, termed synchronizers or *zeitgebers*, the strongest one being the daily light-dark cycle occurring in conjunction with the wake-sleep routine, set the inherited pacemaker circadian timekeeping systems to 24 h each

day. The human circadian time structure was depicted in Figure 1. The circadian variation in systolic blood pressure and heart rate is shown in Figure 2.

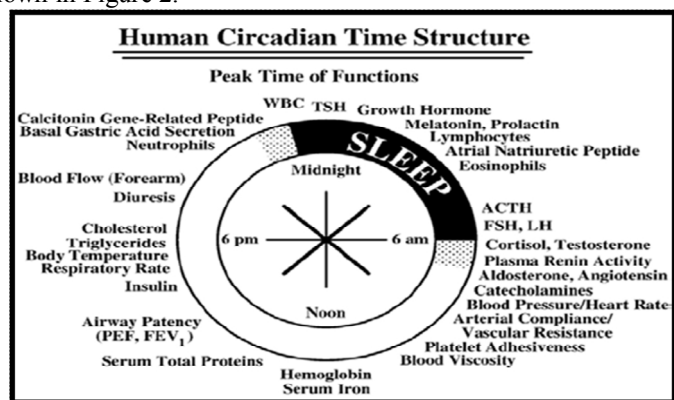


Figure 1: Human circadian time structure. Shown is the approximate peak time of circadian (24-h) rhythms of selected biological variables in persons adhering to a normal routine of daytime activity (~6–7 a.m. to ~10–11 p.m.) alternating with nighttime sleep.

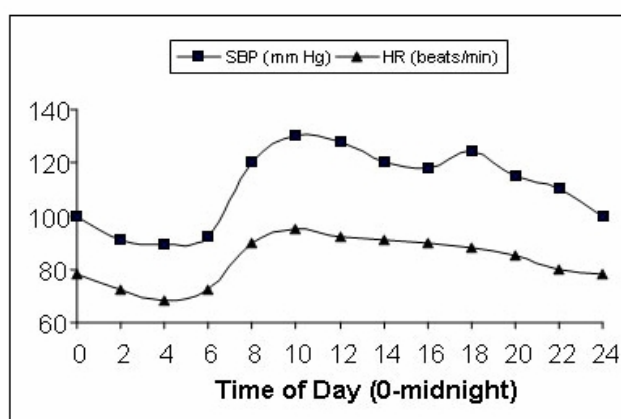


Figure 2: Schematic diagram of circadian variation in systolic blood pressure and heart rate.

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:

- 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.
- 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).
- 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,

hypercholesterolemia 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 patients¹⁵.

Advantages of Chronotherapy

- Chronotherapy is drug-free
- Chronotherapy is more effective when a person sleeps for several hours.
- While Chronotherapy patients often fall asleep this improves their condition and confidence as well.
- Chronotherapy is different from other treatments because it got the beginning, middle, and an end. So one can predict easily the point at which it will work.
- It gives you a new schedule like getting up and sleeping early which will be quite unusual for some days but it will give you a period to adjust psychologically¹⁶.

Disadvantages of Chronotherapy

- It develops a non 24 hours sleep wake syndrome after the treatment as the person sleeps for over 24 hours during the treatment. It's not quite common but the degree of risk is not known.
- Person may also be sleep deprived sometimes.
- Person become less productive during chronotherapy and staying awake till the other schedule will be bit uncomfortable.
- You will have to take some time off from your busy normal schedule as its time taking therapy.
- Medical supervision is mandatory for this therapy. And regular consulting of sleep specialists is recommended.
- One has to keep himself awake till the next sleep schedule. So he has to get himself busy so that he stay awake till the other schedule.
- Person going through the therapy may feel unusually hot or cold sometimes.
- Have to consult the doctor regularly to avoid side effects¹⁷.

Table 1: Various diseases and their chronological behavior

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

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 as shown in Figure 3.

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 etc. 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 plug¹⁸.

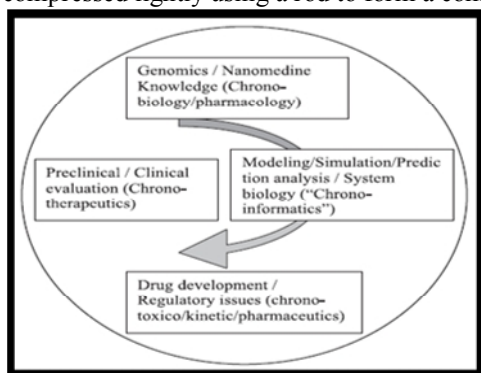


Figure 3: Key steps in designing of chronotropic systems

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 build up 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 forms¹⁹⁻²². 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, e.g. rupture mechanism of double walled tablets is shown in Figure 4. 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 drug²³.

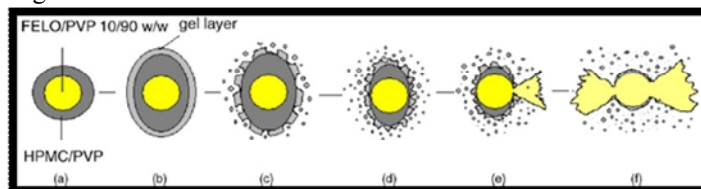


Figure 4: Rupture mechanism of double wall tablets. (a) Initial tablet, (b) gel forming on the coating layer due to the water penetration and tablet swelling (c) erosion inception of the coating layer (d) extended erosion (e) rapture of coating layer and initiation of core dissolution and (f) extended 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 intestine²⁴. Expected behavior and release profile of swellable/erodible reservoir systems for oral pulsatile delivery is depicted in Figure 5.



Figure 5: 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 RS25,26. 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 cannot 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 chronotherapy²⁷.

Stimuli induced pulsatile drug delivery system

These systems are designed on the basis of physiochemical 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 physiochemical 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:

1. Chemical stimuli induced pulsatile drug delivery systems.
2. Temperature induced pulsatile drug delivery systems.
3. 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 the 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 GI tract 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 Eudragit L100 and Eudragit S100 for colonic delivery of indomethacin pellets for chronotherapy of rheumatoid arthritis²⁸.

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. Bae YH et al developed indomethacin pulsatile drug delivery system in temperature range of 20-30°C by using reversible swelling properties of copolymers of N-isopropyl acrylamide and butyrylacrylamide. Kataoka et al developed the thermosensitive polymeric micellies 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 no 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; photo chemically controlled delivery systems prepared by interfacial polymerization of polyamide microcapsules.

CLASSIFICATION OF PULSATILE SYSTEMS

Pulsatile systems can be classified into single and multiple-unit systems. Single-unit systems are formulated either as capsule-based or osmosis-based systems. Single-unit systems are designed by coating the system either with eroding/soluble or rupturable coating. In multiple unit systems, however, the pulsatile release is induced by changing membrane permeability or by coating it with a soluble, erodible, or rupturable membrane.

a) Single-unit pulsatile systems

Single-unit pulsatile systems are further subdivided into capsule based and tablet based systems.

b) Capsule-based systems

❖ Capsular system with a swellable plug

A general architecture of such systems consists of an insoluble capsule body, housing a drug and a plug. The plug is removed after a

predetermined lag time owing to swelling, erosion, and/or dissolution.

The Pulsincap[®] system was developed by RP Scherer International Corporation, MI, USA, in 1990. The system comprises of gelatin capsule body coated with ethyl cellulose to render it impermeable. The molded hydrogel plug was used to seal the drug contents into the capsule body. In the presence of fluids, the hydrogel plug developed a frustoconical shape Figure 6 and slowly pulled itself out of capsule at a controlled rate independent of nature and pH of the medium giving a rapid bulk release²⁹. The lag time was governed by various factors such as length of plug, its insertion distance, and tightness of fit. For water insoluble drugs, a rapid release was ensured by inclusion of effervescent agents or disintegrants. The hydrogel plug consists of insoluble but permeable and swellable polymers (e.g. polymethacrylates), erodible compressed polymers (e.g., hydroxypropylmethyl cellulose, polyvinyl alcohol, polyethylene oxide), congealed melted polymers (e.g., saturated polyglycolated glycerides, glyceryl monooleate), and enzymatically controlled erodible polymer (e.g. pectin)^{30,31}. Ross et al³² used low substituted hydroxypropylcellulose (HPC) in the expulsion system for the release of propranolol over a time period of 2-10 h. This lag could be controlled using compressed erodible tablets made of lactose and HPMC. Krogel and Bodmeier studied the release of chlorpheniramine utilizing the erodible plugs fitted in the capsules. Altering the composition and the weight of the erodible plug could control the release of drug. Stevens et al³³. Designed a hydrophilic sandwich capsule based on a system where the capsule was enclosed within a capsule and the space in between was a gel barrier layer composed of HPMC. When the outer capsule dissolved, the delay in the second pulse was provided by the barrier gel layer.

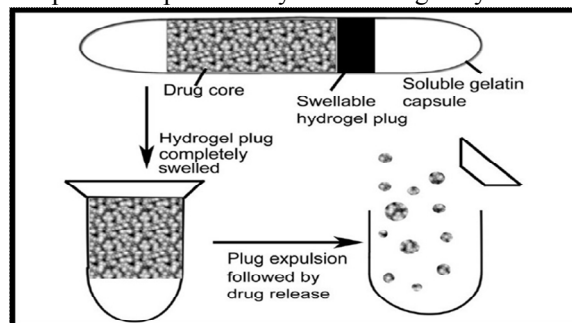


Figure 6: In the presence of fluids, the hydrogel plug developed a frustoconical shape and slowly pulled itself out of capsule at a controlled rate independent of nature and pH of the medium giving a rapid bulk release.

❖ Capsular system based osmosis

The basic appliance in the osmotic system is a capsule enclosed with a semipermeable membrane. Inside the capsule there is an insoluble plug, osmotically active agent, and the therapeutically active agent. When this capsule comes in contact with the body fluid, the semipermeable membrane allows the entry of water, which causes the pressure to develop and the insoluble plug is expelled due to pressure after some lag time³⁴.

The Port[®] System (Therapeutic system research laboratory Ann Arbor, MI, USA) is based on a semipermeable capsule body divided into compartments by a slidable separator Figure 7. The technology achieved made use of a hydrophilic swellable container such as hard gelatin capsule coated uniformly with a layer of a semipermeable membrane. The internal body contained two compartments separated by a nonswellable slider plug. The upper compartment contained immediate release drug, while the lower compartment had an active therapeutic agent with an osmotically active agent. As water diffuses through the semipermeable membrane into the capsule body, osmotic pressure is build up due to solubilization of the osmotically active agent. The hydrostatic pressure developed

pushes the non-swellable plug out as the drug is released in bulk after a desired lag. The technology can be tailored by modifying the thickness of the semipermeable layer and use of different non-swellable separators³⁵. Crison et al. proposed such system to deliver methylphenidate for the treatment of attention deficit hyperactivity disorder in school age children^{36,37}.

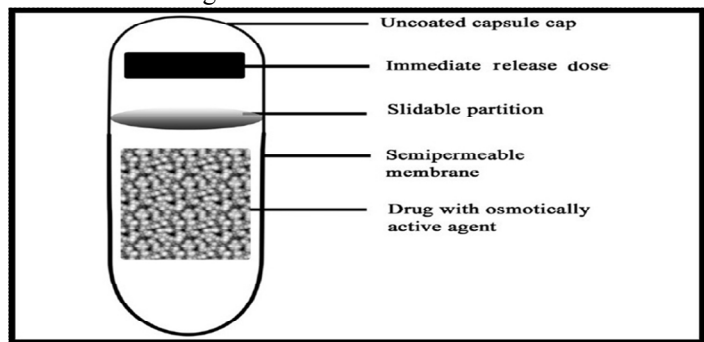


Figure 7: The Port® System (Therapeutic system research laboratory Ann Arbor, MI, USA) is based on a semipermeable capsule body divided into compartments by a slidable separator.

❖ Capsular system based on expandable orifice

The system was designed to deliver drugs as liquid formulations and combine the benefits of extended release with high bioavailability. The liquid formulation is well suited for delivery of insoluble drugs, macromolecules such as polypeptides and polysaccharides. For delivery of such molecules a liquid environment favors solubilization, dispersion, and protection from enzymatic degradation³⁸.

The Liquid OROS Softcap™ developed by Alza Corporation, USA, includes a liquid drug layer, an osmotic engine, push layer, and a semipermeable membrane coating. When the system is in contact with the aqueous environment, water permeates across the rate-controlling membrane and activates the osmotic layer. The expansion of the osmotic layer results in the development of hydrostatic pressure inside the system, thereby forcing the liquid formulation to be delivered from the delivery orifice as shown in Figure 8. The Liquid OROS hardcap™ was framed to accommodate more viscous suspension with higher drug-loading capacity. The lag time can be delayed from 1 to 10 h, depending on the permeability of the rate-controlling membrane and thickness of the barrier layer. A variety of OROS® systems have been developed using this technology such as Procardia XL®, Ditropan XL®, and Concerta®^{39,40,41}.

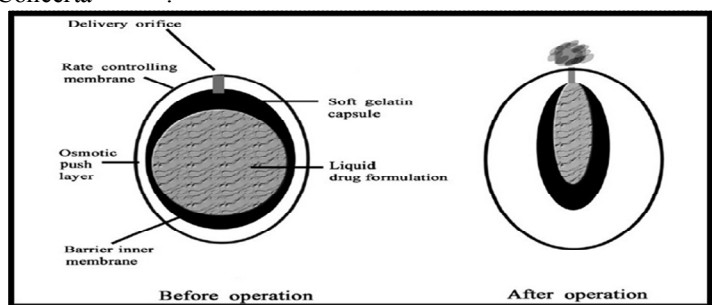


Figure 8: The expansion of the osmotic layer results in the development of hydrostatic pressure inside the system, thereby forcing the liquid formulation to be delivered from the delivery orifice

❖ Delivery by a series of stops

This system is described for implantable capsules. The osmotically driven delivery capsule contains therapeutically active agent and water-absorptive osmotic engine separated by a slider partition to deliver the drug in a pulsatile manner through the orifice as shown in Figure 9. The lag time needed for pulsatile delivery is achieved by a series of stops placed along the inner wall of capsule which obstruct

its movement. As the hydrostatic pressure rises above the threshold level the partition is forced to deliver the next batch of drug. The pulse intensity is controlled by the number of stops and their position along the longitudinal axis⁴².

1. Tablet-based systems

❖ System with erodable or soluble coatings

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

Pozzi et al, (West Pharmaceutical Services Drug Delivery and Clinical Research Centre) developed the Time Clock® pulsed delivery system, which enabled fast and complete release of drug after a predetermined lag time. The core tablet is coated at 75°C with aqueous dispersion of a hydrophobic-surfactant layer (carnauba wax, beeswax, poly (oxyethylene)-sorbitan monooleate). The aqueous dispersion coat is followed by a water soluble coat to improve adhesion to the core coat Figure 10. As the coated tablet comes in contact with aqueous environment, the film rehydrates and redisperses after a certain time lag proportional to the thickness of coat. This approach is used to control the release onset time. Because the drug core is formulated with soluble ingredients, shell dissolution/disintegration becomes the key factor in controlling the lag time. Furthermore, drug release is independent of normal physiological conditions, such as pH, digestive state, and anatomical position at the time of release⁴³⁻⁴⁵.

Chronotropic® system consists of a core containing drug reservoir coated by a hydrophilic polymer HPMC which is responsible for a lag phase. An additional enteric-coated film is given outside this layer to overcome intra-subject variability in gastric emptying rates. The lag time and the onset of action are controlled by the thickness and the viscosity grade of HPMC⁴⁶. A release pattern with two pulses was obtained from a three-layer tablet consisting of two drug-containing layers, separated by a drug-free gellable polymeric barrier layer. The three-layer tablet was coated on three sides with an impermeable coating (ethyl cellulose) and the top side of the tablet remained uncoated. Upon contact with dissolution fluids, the initial dose incorporated into the top layer was released rapidly from the uncoated surface of the tablet. The second pulse was obtained from the bottom layer after the gelled barrier layer (HPMC) had been eroded and dissolved⁴⁷.

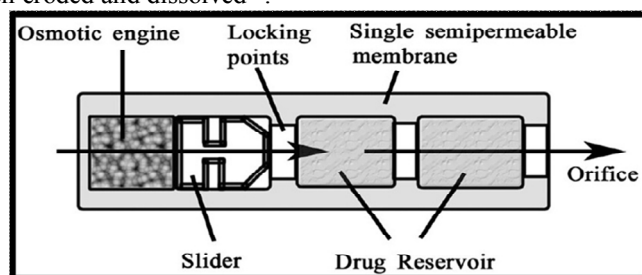


Figure 9: The osmotically driven delivery capsule contains therapeutically active agent and water-absorptive osmotic engine separated by a slider partition to deliver the drug in a pulsatile manner through the orifice.

❖ System with rupturable barrier coatings

These systems are based upon a reservoir system coated with a rupturable membrane. The outer membrane ruptures due to the pressure developed by effervescent agents or swelling agents. Pulsatile release tablet was developed that can suppress release of the drug in the stomach and can release the drug rapidly after a predetermined time of about 3 h in the intestine. The system consists of a core, swelling agent of cross-linked PVP, and a coating film of ethyl cellulose/ Eudragit L. Eudragit L dissolves in an environment of pH above 6 and creates pores in the coating film. Penetration of water molecules from the surroundings through the pores into the

core causes expansion of the swelling agent, bursting the film and releasing the drug with a single pulse. Manipulation of the thickness of coating film can control the lag time⁴⁸.

2. Multi-unit pulsatile systems

Multiparticulate dosage forms offer more reliability when compared to single-unit dosage forms. The potential benefits offered such as predictable gastric emptying, no risk of dose dumping, flexible release patterns, and increase bioavailability with less intra and inter subject variability. Multiparticulate systems are further classified as systems based upon change in membrane permeability and systems based upon rupturable coating.

e) Reservoir systems with rupturable polymeric coatings

Multiparticulate drug dosage forms are composed of small beads, each small bead further comprised many layers. Some layers contain drug substance, while others are rate-controlling polymers. With the multiparticulate system, customized drug release profiles are created by first layering active drug onto an inert core (such as a cellulose sphere), then applying one or more rate-controlling, functional polymers, to produce spherical, multi-layered particles. The drug-layering process can be conducted either from aqueous or solvent-based drug solutions. Many release profiles can be achieved using this approach-including sustained release, time-delayed release, and pulsatile release of active pharmaceutical ingredients for absorption throughout the GI tract. Time-delayed release of the drug as either a burst or sustained release profile can be achieved over a period of 1-12 h, with a lag time of 4-10 h. The duration of drug release following the lag-time depends on the composition and thickness of the polymer barrier and the lag-time coating itself. The multiparticulate system provides optimal release profiles for either single drugs or for a combination of drugs^{49,50}.

Ueda et al.⁵¹⁻⁵⁴ developed a time-controlled explosion system (TES), where drug is released by explosion of the outer membrane. TES was developed for multiple-unit dosage forms consists of a core drug plus an inert osmotic agent and suitable disintegrates. The osmotic pressure build up by water ingress causes the core to explode, with an immediate release of the drug. The explosion of formulation can also be achieved through use of swelling agents.

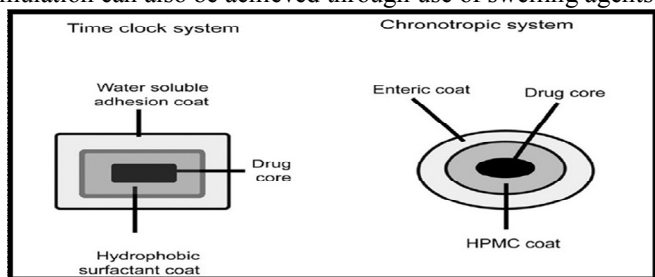


Figure 10: The aqueous dispersion coat is followed by a water soluble coat to improve adhesion to the core coat.

f) Reservoir systems with soluble or eroding polymer coatings

Another class of reservoir-type multiparticulate pulsatile systems is in which the barrier dissolves or erodes after a specific lag time followed by burst release of drug from the reservoir core. The lag time in such systems is controlled by the thickness of the coating layer. The basic principle employed in these systems is that of pH-sensitive polymers complimenting to their large increase in solubility at some point in the GI tract.

Gazzaniga et al.⁵⁵ developed a multi-unit system with a reservoir drug coated with a high viscosity polymer (HPMC 4000) and an

outer enteric coating. The outer film protects the system from the fluids in the stomach and dissolves on entering the small intestine. HPMC layer delays the release of drug for 3-4 h when the system is transported through small intestine. Another system was developed containing multicoated multiparticulates for time controlled pulsatile release. One of the coating membranes is an enteric polymer and the second membrane barrier is a mixture of a water-insoluble polymer and an enteric polymer. An organic acid, such as fumaric acid, citric acid, succinic acid, tartaric acid, or malic acid, may be provided between the first and second membrane layers to provide for the time-separated pulses. The acids in between the membranes may delay the dissolution of the enteric polymer in the inner layer, thereby increasing the lag time as well as decreasing the rate of release of the active ingredient from the coated microparticulates⁵⁶.

g) Systems with changed membrane permeability

The release profile in this system depends on physico-chemical properties of drug and its interaction with the membrane. A sigmoidal release pattern obtained in this system is based on the permeability and water uptake of Eudragit RS or RL and is influenced by the presence of different counter-ions in the release medium. Narisawa et al.^{57,58} has developed a device capable of pulse release depending on the change in diffusion properties of Eudragit RS. They found that a core of theophylline coated with Eudragit RS showed very slow release rates in pure water but a significant increase in the release rate was found when the microcapsules were immersed in an organic acid solution containing succinic, acetic, glutaric, tartaric, malic, or citric acid. This was due to higher hydration of the film containing quaternary ammonium groups on interaction with the acids. Another such system was reported in which theophylline and sodium acetate acting as permeability modifiers were layered on the pellets followed by a coat of Eudragit RS30D. The lag time was increase with increasing thickness of the outer membrane⁵⁹⁻⁶¹.

MARKETED TECHNOLOGIES

There are various types of pharmaceutical technologies used for the preparation of drugs for chronotherapy⁶²⁻⁶⁴. Technologies used for the parenteral route in chronotherapy include the use of chronomodulating infusion pumps (Panomat™) and controlled release microchip strategies. And technologies used for oral administration are-Ceform™. There are other methods like three dimensional printing (3dp) which includes usage of erodible polymers for the controlled release and changing the physiochemical properties of the drug. The most recent was the floating pulsatile system using high internal phase emulsion based porous material for chronotherapy⁶⁵. Low density floating multiparticulate pulsed release dosage forms are also available⁶⁶. The desired release of ranitidine hydrochloride from the tablet with a coating successfully explains the combined principles of floating and pulsatile used in chronotherapy⁶⁷. Many marketed products in the form of transdermal drug delivery system having chronopharmaceutical applications are available⁶⁸; some of them are ChronoDose™, crystal reservoir⁶⁹ and thermo responsive membrane systems⁷⁰. For rectal route-aminophylline delivery system was reported and many novel chronopharmaceuticals has been used for this purpose⁷¹. Some of the marketed technologies of pulsatile drug delivery are mentioned in table 2

Table 2: Marketed technologies of pulsatile drug delivery

Technology	Mechanism	Proprietary name and dosage form	API	Disease
OROS®;	Osmotic Mechanism	Covera-HS® XL Tablet	Verapamil HCl	Hypertension
CODOS®	multiparticulate ph dependent system	Verelan® PM; XL release capsule	Verapamil HCl	Hypertension
DIFFUCAPS®	multiparticulate system	Innopran®;XL tablets	Verapamil HCl, propranolol HCl	Hypertension
Three dimensional printing®	externally regulated system	TheirForm®	Diclophenac sodium	Inflammation
PulsincapTM	Rupturable system	PulsincapTM	Dofetilide	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. If drug released is designed in a time controlled manner and maximum drug is made available at peak time, optimization of the therapy can be achieved for diseases that follows the circadian rhythm. Chronopharmaceutics assures improved patient outcome and optimized disease management in the future. Dependence of response over human action to trigger the drug release is the major drawback associated with these systems. Hence, 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). 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 physiochemical properties), the ease of manufacturing, the cost-effectiveness, and the flexibility in the pharmacokinetic profile. In near future due to more advancement of technology, the hurdles in manufacturing and processing steps will be overcome and a number of patients will be greatly benefited by these systems.

ACKNOWLEDGMENT

The authors are thankful to Maratha Mandal's college of pharmacy for providing facilities and support.

REFERENCES

- Shaked, Z, McGinity, J, Pharmaceutical formulation containing DFMO for the treatment of cancer: US Patent 6277411 (2001).
- Bramha N. Singh. Modified- release formulation for colonic delivery. Recent Patents on Drug Delivery and Formulation. 2007; 1:53-63.
- Borody TJ, Shortis WG, Shortis NP. Picosulfate-containing preparation for colonic evacuation: US5858403 (1999).
- Halskov S, Jepsen SK. Composition for use in the regulation of subnormal pH values in the intestinal tract and for treatment of bowel diseases: US5716648 (1998).
- Singh BN, Kim, KH. In: Swarbrick J, Boylan JC (Eds.). Encyclopedia of Pharmaceutical Technology, New York, Marcel Dekker, Inc. 2002; 886-909.
- Nirav Patel, Jayvandan Patel, Tejal Gandhi, Tejal sonil, Shreeraj shah. Novel pharmaceutical approaches for colon specific drug delivery: An overview. Journal of Pharmacy Research. 2008; 1(1):2-10.
- Deepak Prashar, Hemant Mittal, Rakesh Kumar. Hydrocolloids based colon specific drug delivery system. Asian Journal of Biochemical and Pharmaceutical Research. 2011; 1(3):144-154.
- Asha Patel, Nilam Bhatt, Dr.KR Patel, Dr. NM Patel, Dr. MR Patel. Colon targeted drug delivery system: a review system. Journal of Pharmaceutical Science and Bioscientific Research. 2011; 1(1):37-49.
- Manivannan Rangasamy. Colon targeted drug delivery systems: a review. International Journal of Drug Formulation and Research. 2010; 1(2):30-54.
- Basit A, Bloor J. Perspective on colonic drug delivery. Business briefing: Pharmatech. 2003; 185-190.
- Youan BC. Chronopharmaceutics: Gimmick or clinically relevant approach to drug delivery: review. Journal of Controlled Release. 2004; 98:337-352.
- Ohdo S, Koyanagi S, Suyama H, Higuchi S, Aramaki H. Changing the dosing schedule minimizes the disruptive effects of interferon on clock function. Nat. Med. 2001; 7:356-360.
- Belgamwar VS, Gaikwad MV, Patil GB, Surana S. Pulsatile drug delivery system. Asian Journal of Pharmaceutics. 2008; 141-145.
- Maronde E, Stehle EH. The mammalian pineal gland: known facts, unknown facets, Trends Endocrinol. Metab. 18. 2007; 142–149.
- Sharma S, Pawar A. Low density multiparticulate system for pulsatile release of meloxicam. International Journal of Pharmaceutics. 2006; 313:150-158.
- Stael B. When the clock stops ticking, metabolic syndrome explodes. Nat. Med. 2006; 12:54–55.
- Smolensky MH, D'Alonzo GE. Medicalchronobiology: concepts and applications. Am Rev Respir Dis. 1993; 147(6):S2-19.
- Gohel MC, Sumitra MG. Modulation of active pharmaceutical material release from a novel 'tablet in capsule system' containing an effervescent blend. Journal of Controlled Release. 2002; 79:157-164.
- Ueda Y, Hata T, Hisami Y, Ueda S, Kotani M. Time controlled explosion systems and process for preparing the same. U.S. Patent (4871549) 1989.
- Ueda S, Hata T, Yamaguchi H, Kotani M, Ueda Y. Development of a novel drug release system, time controlled explosion system (TES): I. Concept and design. Journal of Drug Target. 1994; 2:35-44.
- Ueda S, Yamaguchi H, Kotani M, Kimura S, Tokunaga Y, Kagayama A, Hata T. Development of a novel drug release system, time-controlled explosion system (TES): II. Design of multiparticulate TES and in-vitro drug release properties. Chemical Pharma Bulletin. 1994; 42:359-363.
- Ueda S, Yamaguchi H, Kotani M, Kimura S, Tokunaga Y, Kagayama A, Hata T. Development of a novel drug release system, time-controlled explosion system (TES): III. Relation between lag time and membrane thickness. Chemical Pharma Bulletin. 1994; 42:364-367.
- Roy P, Shahiwala A. Multiparticulate formulation approach to pulsatile drug delivery: current perspectives. Journal of Controlled Release. 2008; 134:74-80.
- Gazzaniga A, Iamartino P, Maffione G, Sangalli ME. Oral delayed-release system for colonic specific delivery. International Journal of Pharmaceutics. 1994; 108:77-83.
- Narisawa S, Nagata M, Danyoshi C, Yoshino H, Murata K, Hirakawa Y, Noda K. An organic acid induced sigmoidal release system for oral controlled release preparation. Pharmaceutical Research. 1993; 11:111-116.
- Narisawa S, Nagata M, Hirakawa Y, Kobayashi M, Yoshino H. An organic acid induced sigmoidal release system for oral controlled release preparations. Journal of Pharmaceutical Sciences. 1996; 85:184-188.
- Badave SS, Sher P, Korde A, Pawar AP. Development of hollow/ porous calcium pectinate beads for floating-pulsatile drug delivery. European Journal of Pharmaceutics and Biopharmaceutics. 2007; 65:85-93.
- Akhgari A, Garekani HA, Sadeghi F, Azimaie M. Statistical optimization of indomethacin pellets coated with pH dependent methacrylic polymers for possible colonic drug delivery. International Journal of Pharmaceutics. 2005; 305:22-30.
- Stevens H. Pulsincap and hydrophilic sandwich. In: Rathbone M, Hadgraft J, Roberts M. Modified-release drug delivery technology. London: Informa Health Care. 2003; 257-60.
- Kroegel I, Bodmeier R. Pulsatile drug release from an insoluble capsule body controlled by an erodible plug. Pharmacy Research. 1998; 15:474-81.
- Kroegel I, Bodmeier R. Evaluation of an enzyme containing capsular shaped pulsatile drug delivery system. Pharmacy Research. 1999; 16:1424-9.
- Ross A, Macrae R, Walther M, Stevens H. Chronopharmaceutical drug delivery from a pulsatile capsule device based on programmable erosion. J Pharm Pharmacol. 2000; 52:903-9.
- Stevens H, Ross A, Johnson J. A novel oral probe formulation: The Hydrophilic Sandwich (HS) capsule. Journal of Pharmacy and Pharmacology. 2000; 52:41.
- Belgamwar V, Gaikwad M, Patil G, Surana S. Pulsatile drug delivery system. Asian Journal of Pharmacy. 2008; 2:141-5.

36. Crison J, Vieira. New Approaches for optimizing Oral drug delivery: Zero-order sustained release to pulsatile immediate release using the Port System. In: Rathbone M, Hadgraft J, Roberts M. Modified-release drug delivery technology. London: Informa Health Care. 2003; 253-61.
37. Crison J, Vieira M, Kim J, Siersma C, Amidon G, Pulse delivery of methylphenidate indogs using an osmotic drug delivery system. Proc Intern Symp Control Rel Bioact Mater. 2001; 28: 6101.
38. Medicalnewstoday.com. New York. MediLexicon International Ltd © 2009 [updated 2009 July 16; cited 2009 Aug 9] Available from: <http://www.medicalnewstoday.com>.
39. Patrick S, Wong L, Gupta S, Stewart B. Osmotically controlled tablets. In: Rathbone M, Hadgraft J, Roberts M. Modified-release drug delivery technology. London: Informa Health Care. 2003; 113.
40. Patrick S, Martin A. Drug delivery. In: Martin A, editor. Martin's physical pharmacy and pharmaceutical sciences. New York: Lippincott Williams and Wilkins. 2005; 670.
41. Dong L, Shafi K, Wong P, Wan J. L-OROS® SOFTCAP™ for controlled release of nonaqueous liquid formulations. Journal of Drug Delivery. 2002; 2:1.
42. Sharma S. Osmotic controlled drug delivery system. Latest Rev. 2008; 6:3.
43. Balaban SM, Pike JB, Smith JP, Baile CA. Osmotically driven delivery devices with pulsatile effect: US Patent No. 5209746 (1993) May 11.
44. Wilson C, Shah H, Programmed drug delivery systems and the colon. In: Rathbone M, Hadgraft J, Roberts M. Modified Release Drug Delivery Systems, London: Informa Health Care. 2007; 141.
45. Kem.edu. Mumbai. [updated 2009 July 16; cited 2009 Aug 9] Availablefrom: www.kem.edu.
46. Sandrine B, Richard H, Elias F. Polymer colon drug delivery systems and their application to peptides, proteins, and nucleic acids. American Journal of Drug Delivery. 2005; 34:171-204.
47. Anal A. Time-controlled pulsatile delivery systems for bioactive compounds. Recent Patents Drug Delivery and Formulation. 2007; 1:73-79.
48. Fan T, Wei S, Yan W. An investigation of pulsatile release tables with ethylcellulose and Eudrajit L as film coating materials and crosslinked polyvinyl pyrrolidone in the core tablets. Journal of Controlled Release. 2001; 7:245-51.
49. Eurand.com. New York: Eurand c 2002-2009 [updated 2009 July 16; cited 2009 Aug 9] Available from <http://www.sysrevpharm.org>.
50. Roy P, Shahiwala A. Multiparticulate formulation approach to pulsatile drug delivery: Current perspectives. Journal of Control Release. 2009; 134:74-80.
51. Ueda Y, Hata T, Hisami Y, Ueda S, Kodani M. Time controlled explosion system and process for the preparation of same: US Patent no.4871549 (1989) Oct 3.
52. Ueda S, Hata T, Yamaguchi H, Kotani M, Ueda Y. Development of a novel drug release system, time controlled explosion system (TES): I: Concept and design. Journal of Drug Target. 1994; 2:35-44.
53. Ueda S, Yamaguchi H, Kotani M, Kimura S, Tokunaga Y, Kagayama A, et al. Development of a novel drug release system, time-controlled explosion system (TES): II: Design of multiparticulate TES and in vitro drug release properties. Chemical Pharma Bulletin. 1994; 42:359-63.
54. Ueda S, Yamaguchi H, Kotani M, Kimura S, Tokunaga Y, Kagayama A, et al. Development of a novel drug release system, time-controlled explosion system (TES): III: Relation between lag time and membrane thickness. Chemical Pharma Bulletin. 1994; 42:364-7.
55. Gazzaniga A, Iamartino P, Maffione G, Sangalli M. Oral delayed-release system for colonic Specific delivery. International Journal of Pharmaceutics. 1994; 10:77-83.
56. Sher P, Ingavle G, Ponrathnam S, Pawar A. Low density porous carrier based conceptual drug delivery system. Microporous Mesoporous Mater. 2007; 102:290-8.
57. Narisawa S, Nagata M, Hirakawa Y, Danyoshi C, Yoshino H, Murata K. An organic acid induced sigmoidal release system for oral controlled release preparation. Journal of Pharmacy Research. 1993; 11:111-6.
58. Narisawa S, Nagata M, Hirakawa Y, Kobayashi M, Yoshino H. An organic acid induced sigmoidal release system for oral controlled release preparations: 2, Permeability enhancement of Eudragit RS coating led by the physico-chemical interactions with organic acid. Journal of Pharmaceutical Science. 1996; 85:184-8.
59. Bussemer T, Bodmeier R, Drug delivery-Pulsatile systems. In: Swarbrick J, Boylan J. Encyclopedia of pharmaceutical technology, London. 2004; 106.
60. Kalantzi L, Karavas E, Koutris E, Bikiaris D. Recent advances in oral pulsatile drug delivery. Recent Pat Drug Deliv Formul. 2009; 3:49-63.
61. Rathod S. Colon targeted pulsatile drug delivery: A review. Latest Rev. 2007; 5:2.
62. Youan BBC. Chronopharmaceutics: Science and Technology for Biological Rhythm Guided Therapy and Prevention of Diseases, John Wiley & Sons, Hoboken, NJ, USA. 2009.
63. Youan BBC., Chronopharmaceutics: gimmick or clinically relevant approach to drug delivery. Journal of Control Release. 2004; 98:337-353.
64. Khan Z, Pillay V, Choonara YE, du Toit LC, Drug delivery technologies for chronotherapeutic applications. Pharmarmaceutical Delevry and Technology. 2009; 14:602-612.
65. Sher P, Ingavle G, Ponrathnam S., Benson JR, Li NH, Pawar AP., Novel/ conceptual floating pulsatile system using high internal phase emulsion based porous material intended for Chronotherapy. AAPS Pharm Sci Tech. 2009; 10:1368-1380.
66. Roy P, Shahiwala A, Multiparticulate formulation approach to pulsatile drug delivery: current perspectives. Journal of Control Release. 2009; 134:74-80.
67. Roy P, Shahiwala A, Statistical optimization of ranitidine HCl floating pulsatile delivery system for chronotherapy of nocturnal acid breakthrough. European Journal of Pharmaceutical Science. 2009; 37: 363-369.
68. Hradetzky D. Transdermal drug delivery devices for Chronotherapy. Med. Device Technol, 2008; 19:45-47.
69. Kato H, Nagata O, Yamazaki M, Suzuki T, Nakano Y, Development of transdermal formulation of tulobuterol for the treatment of bronchial asthma. YakugakuZasshi. 2002; 122:57-69.
70. Lin SY, Ho CJ, Li MJ. Precision and reproducibility of temperature response of a thermo-responsive membrane embedded by binary liquid crystals for drug delivery. Journal of Control Release. 2001; 73:293-301.
71. Shiohira H, Fujii M, Koizumi N, Kondoh M, Watanabe Y, Novel chronotherapeutic rectal aminophylline delivery system for therapy of asthma. International Journal of Pharmacy. 2009; 379:119-124.