

Advancement In Chronotherapeutic Drug Delivery System: Marketed Technologies And Current Scenario

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Abstract

Traditionally, drugs are released in an immediate or extended fashion. However, in recent years, pulsatile drug release systems are gaining growing interest. These systems are designed according to the circadian rhythm of the body that are to be dosed at bed time but show rapid and complete drug release after a lag time during early morning hours in order to enhance therapeutic outcomes and reduce side effects. It is also known as Chronotherapeutic drug delivery system and it focuses on the release of a drug at specific time and at a specific site in order to maintain constant blood levels of an appropriate drug. These systems are beneficial for the drugs having chronopharmacological behavior where night time dosing is required and for the drugs having high first-pass effect and having specific site of absorption in gastrointestinal tract. Many disease like hypertension, asthma, peptic ulcer, hypercholesterolemia, arthritis and attention deficit syndrome in children may be better controlled and treated by pulsatile drug delivery system, because in such type of system drug is released in a programmed manner. The purpose of writing this review on pulsatile drug delivery systems (PDDS) is to compile the recent literature with special focus on the different recent technologies involved in the development of the formulation.

Keywords: Circadian rhythm, Lag time, Chronotherapeutic drug delivery system, Pulsatile drug delivery system, Chronopharmacological

INTRODUCTION

Pulsatile drug delivery system is a type of intelligent drug delivery system which is suitable for regulating drug release rates in a response to physiological demand. Pulsatile drug delivery system is also known as Chronotherapeutic drug delivery system. PDDS is defined as the rapid and transient release of a certain amount of molecules within a short time period immediately after a predetermined off-released period, i.e., lag time. The pulsatile drug delivery aims to release drug on programmed pattern i.e. at right time and at the right site of action.^[1,2,3] These systems are delineated according to the circadian rhythm of the body. Circadian rhythm regulates many body functions like metabolism, physiology, behaviour, sleep patterns, hormone production, etc. Many diseases such as cardiovascular, asthma, peptic ulcer, arthritis etc. follow the body's circadian rhythm and shows circadian pattern.^[4] It has been reported that more shocks and heart attacks occur during morning hours. Blood pressure is also reported to be high in the morning till late afternoon, and then drops off during night. Patients suffering from osteoarthritis are reported to have less pain in the morning than night, while patients suffering from rheumatoid arthritis feel more pain in the morning hours. Pulsatile drug delivery systems are attain a lot of interest and attention these days. These systems have a unique mechanism of delivering the drug rapidly and completely after a "lag time," i.e., a period of "no drug release."^[5] The pulsatile drug delivery system are advantageous for drugs having high first-pass effect; drugs delivered for diseases that follow chronopharmacological behavior; drugs having specific absorption site in GIT, targeting to colon; and cases where night time dosing is required.^[6]

ADVANTAGES OF PULSATILE DRUG DELIVERY SYSTEM

1. Extended daytime or nighttime activity
2. Reduced side effects

3. Reduced dosage frequency
4. Reduction in dose size
5. Improved patient compliance
6. Lower daily cost to patient due to fewer dosage units are required by the patient in therapy.
7. Drug adapts to suit circadian rhythms of body functions or diseases.
8. Drug targeting to specific site like colon.
9. Protection of mucosa from irritating drugs.
10. Drug loss is prevented by extensive first pass metabolism.
11. Patient comfort and compliance.^[7,8]

NECESSITIES OF PULSATILE DRUG DELIVERY SYSTEM

Circadian rhythm:

Many body functions that follow circadian rhythm. e.g.: Secretion of hormones, acid secretion in stomach, gastric emptying, and gastrointestinal blood transfusion. Chronopharmacotherapy of diseases which shows circadian rhythms in their pathophysiology like bronchial asthma, myocardial infarction, angina pectoris, rheumatic disease, ulcer, and hypertension.^[9,10]

First pass metabolism:

The drugs that undergo extensive first-pass metabolism (β -blockers) and those that are characterized by idiosyncratic pharmacokinetics or pharmacodynamics resulting in reduced bioavailability, altered drug/metabolite ratios, altered steady state levels of drug and metabolite, and potential food-drug interactions require delayed release of the drug to the extent possible.^[11]

Biological tolerance:

Drugs that produce biological tolerance and hence demand for a system that will prevent their continuous presence at the site of action as this tends to reduce their therapeutic effect. **Protection from gastric environment:**

It is essential for the drugs that undergo degradation in gastric acidic medium (e.g., peptide drugs), irritate the gastric mucosa (NSAID) or induce nausea and vomiting.

Time dependent:

Many body functions follow circadian rhythm, i.e., their activity increases or decreases with time. Severity of diseases like bronchial asthma, myocardial infarction etc are also time dependent.

Local therapeutic need:

For the treatment of local disorders such as inflammatory bowel disease, the delivery of compounds to the site of inflammation with no loss due to absorption in the small intestine is highly desirable to achieve the therapeutic effect.^[12,13]

SUCCESSFULLY MARKETED CHRONOTHERAPEUTIC DRUG DELIVERY SYSTEM

Chronopharmaceutics is composed of two words pharmacetics and chronobiology. Chronobiology is the study of biological rhythms and their mechanisms.^[14] Chronobiology deals with the study of three types of biorhythms affecting the human body. These are as follows:

Ultradian: Cycles shorter than a day. For example, the milliseconds, it takes for a neuron to fire, or a 90 mins sleep cycle.

Infradian: Referring to cycles longer than 24 hours. For example, monthly menstruation.

Circadian rhythm: Biological rhythm within a single day is termed as circadian rhythm. Here, the oscillation time is 24 hours.^[15] Out of four biological rhythms, circadian rhythm is the main rhythm in our body which regulates all the physiological, chemical, biological and behavioral processes.^[16]

DISEASES REQUIRING PULSATILE DRUG DELIVERY

The potential advantages of chronotherapeutics have been demonstrated in the management of a number of diseases. In particular there is a great deal of interest in how chronotherapy can particularly benefit patients suffering from rheumatoid arthritis and related disorders, like, asthma, cancer, cardiovascular diseases and peptic ulcer disease.^[17]

DISEASES	CHRONOLOGICAL BEHAVIOR	DRUGS USED
Cardiovascular disease	BP is at the lowest during sleep cycle and rises steeply during the early morning awakening days.	Nitro-glycerin, Calcium channel blocker, ACE inhibitors
Hypercholesterolemia	Cholesterol synthesis is generally higher during night than during day time.	HMG CoA reductase Inhibitors
Peptic ulcer	Acid secretion is high in the afternoon and at night	H2 blockers
Asthma	Precipitation of attacks during night or at early morning hour	β2agonist, Antihistaminic
Diabetes mellitus	Increase in blood sugar level after meal	Sulfonylurea, Insulin, biguanid

Table 1. Diseases required pulsatile drug delivery^[11]

RECENTLY AVAILABLE DIFFERENT MARKETED TECHNOLOGIES OF PULSATILE DRUG DELIVERY

1. SODAS Technology (Spheroidal Oral Drug Absorption System)

A SODA is Elan's Multiparticulate drug delivery system.^[18] Based on the production of controlled release beads, the SODAS technology is characterized by its inherent flexibility, enabling the production of customized dosage forms that respond directly to individual drug candidate needs.^[19] Elan's SODAS Technology is based on the production of uniform spherical beads of 1-2 mm in diameter containing drug plus excipients and coated with product specific controlled release polymers.^[20] The most recent regulatory approvals for SODAS based system occurring with the launch of once-daily oral dosage forms of Avinz, Ritalin LA and Focalin XR.^[21]

2. TCES (Time Control Explosion System)

It is useful for the water insoluble drug. This invention mainly relates to controlled absorption drug delivery systems and more particularly to combine coating dissolution and explosion mechanism in coated drug containing pellets for assured timely release of orally administered pharmaceuticals. The lag time is related to the thickness of the membrane. Pellets enclosed in capsule. Each pellet release the drug at different time in said environment when the capsule is get disintegrates. Each pellet core part contains drug and swelling agent. Core part is surrounded by the water permeable membrane, which prevent the release of the drug in to environment.^[22,23,24]

3. IPDAS Technology (The Intestinal Protective Drug Absorption System)

The IPDAS is a high density multiparticulate tablet technology, intended for use with GI irritant compounds. IPDAS was initially developed as part of the development process for Elan's proprietary naproxen formulation, Napreelan. The objective was to develop a once daily controlled release system that would have a fast onset of action and reduced gastric irritancy. The IPDAS technology is composed of numerous high density controlled release beads, which are compressed into a tablet form. Once an IPDAS tablet is ingested, it rapidly disintegrates and disperses beads containing a drug in the stomach, which subsequently pass into the duodenum and along the gastrointestinal tract in a controlled and gradual manner, independent of the feeding state. Release of active ingredient from the multiparticulate occurs through a process of diffusion either through the polymeric membrane and or the micro matrix of polymer/active ingredient formed in the extruded/spheronized multiparticulates.^[21]

4. OSDrC Technology (One Step Dry Coating)

OSDrC technology opens the door to new world of pharmaceutical tablet manufacturing. The key word in this new world is "unique", "High quality", "low cost" and "Innovative". The OSDrC rotary tableting machine, with its variable double-punch configuration, supports single-step manufacturing of pharmaceutical products. In addition to the commercial-scale production of conventional cored (tablet-within-a-tablet) tablets, this machine is ideal for manufacturing a variety of high-quality drug products at

low cost. This innovative technology can also replace conventional sugar and film-coated tablets. This technology allow production scientist to devise new novel dosage forms and align capability with scientific creativity.^[10] OSDrC technology allows placement of any number of cores of any shape into the tablet just where they need to be positioned for optimum delivery of active pharmaceutical ingredients.^[25]

5. GEOMATRIX Technology

The Geomatrix technology is applied to achieve customized levels of controlled release of specific drugs and can achieve simultaneous release of two different drugs and different rates from a single tablet. The controlled release is achieved by constructing a multilayered tablet made of two basic key components:

1) Hydrophilic polymers such as hydroxypropyl methylcellulose (HPMC)

2) Surface controlling barrier layers.

Active loaded core surface that is available for drug release when exposed to the fluid is controlled by barrier layers. The combination of layers, each with different rates of swelling, gelling and erosion, is responsible for the rate of drug release within the body. When first swallowed, for example, the drug concentration is high but the surface area low. As time progresses the core swells and the surface area increases to compensate for the decrease in drug concentration. One of the major benefits of the Geomatrix technology is its ability to be easily incorporated into the production line. The Geomatrix tablets can be manufactured by readily available equipment that can be integrated into widely-used pharmaceutical processes, thus giving firms more control over their own production activities.^[21]

6. ACCU-BREAK Technology

Accu-Break Pharmaceuticals, Inc. and Azopharma Product Development Group, Inc. have provided exciting new product development opportunities. Accu-Break Pharmaceuticals is a pharmaceutical technology development company with a suite of proprietary tablet technologies. The patented Accu-Break tablet designs are intended to provide physicians and patients with easily divisible tablets that when divided, result in exact smaller doses for ease of customizing treatment through dose adjustment and titration. Accu-Break tablets are manufactured on commercially available multilayer compression equipment. AccuBreak Technology is divided in to two types ACCU-B Technology and ACCU-T Technology.^[26]

7. ACCU-T CR Tri Layer Tablets

ACCU-T CR (controlled release) Tri-Layer Tablets configuration applies controlled release technology to further enhance treatment options. The ACCU-T CR tablet contains controlled release medication at either end of the tablet separated by a drugfree break layer, allowing the CR dose to be divided into exact half doses without affecting the rate of drug release. The majority of conventional CR tablets are not suited for subdividing due to the increase of surface area and the subsequent change in release kinetics. ACCU-T technology provides a solution to this problem and introduces dose flexibility into CR dosage forms.

Additionally, an IR (immediate release) component can be added to CR tablets to add even more treatment options and potential product capabilities.^[26]

8. CODAS Technology (Chronotherapeutic Oral Drug Absorption System)

In certain cases immediate release of drug is undesirable. A delay of drug action may be required for a variety of reasons. Chronotherapy is an example of when drug release may be programmed to occur after a prolonged interval following administration. Elan's Chronotherapeutic Oral Drug Absorption System (CODAS Technology) was developed to achieve this prolonged interval^[27]. Elan's drug delivery technology can be tailored to release drug after a predetermined delay. The CODAS drug delivery system enables a delayed onset of drug release, resulting in a drug release profile that more accurately compliments circadian patterns^[28,29]

9. PRODAS Technology (Programmable Oral Drug Absorption System)

PRODAS is a multiparticulate technology, which is unique in that it combines the benefits of tableting technology within a capsule. The PRODAS delivery system is presented as a number of minitabets combined in a hard gelatin capsule. Very flexible, the PRODAS technology can be used to pre-program the release rate of a drug. It is possible to incorporate many different minitabets, each one formulated individually and programmed to release drug at different sites within the gastro-intestinal tract. It is also possible to incorporate minitabets of different sizes so that high drug loading is possible.^[30]

10. TMDS Technology (Time Multiple Action Delivery system)

TMDS Technology provide control release rate of multiple ingredient within single tablet in programmed manner. TMDS Technology allows for more than one active ingredient in a single tablet formulation provide multiple release profile over extended period of time.^[31]

11. DMDS Technology (Dividable Multiple Action Delivery System)

DMDS is designed to provide greater dosing flexibility that improve product efficacy and reduces side effects. Traditional controlled release tablet often lose their controlled release mechanism of delivery once it broken. But DMDS technology allows tablet to be broken down in half so that each respective portion of the tablet will achieve exactly the same release profile as the whole tablet.^[32]

12. PMDS Technology (Programmed Multiple-action Delivery System)

PMDS technology is designed to provide for the multi-phasic delivery of any active ingredient in a more controlled fashion as compared to typical controlled release technologies. Our PMDS technology is designed to allow for the release of the active ingredient at predetermined time intervals and desired levels on a consistent basis. This technology allows us to overcome one of the technical challenges in the development of multi-particulate dosage forms – achieving acceptable uniformity and reproducibility of a product with a variety of release rates.

It is designed to provide greater dosing flexibility that improves product efficacy and may reduce side effects.

13. GEOCLOCK Technology

The concept is designed on the basis of Geomatrix technology. Skye Pharma developed a new oral drug delivery technology. Geoclock tablets have an active drug inside an outer tablet layer consisting of a mixture of hydrophobic wax and brittle material in order to obtain a pH independent lag time prior to core drug delivery at a predetermined release rate. This dry coating approach is designed to allow the timed release of both slow release and immediate release active cores by releasing the inner table first after which time the surrounding outer shell gradually disintegrates. As well as controlled release, the Geoclock technology also has applications for the improved release of colonic drug delivery, as well as multiple pulse drug delivery to deliver doses of the drug at specific times throughout the day.^[19]

14. PULSYS Technology

The PULSYS dosage form is a compressed tablet that contains pellets designed to release drug at different regions in the gastro-intestinal tract in a pulsatile manner. The dosage form is made up of multiple pellet types of varying release profiles that are combined in a proportion so as to produce a constant escalation in plasma drug levels in the early portion of the dosing interval. The transit properties of pellets enhance the overall absorption-time window and offer improved bioavailability compared to tablet matrix forms.^[33,34]

15. Magnetic Nanocomposite Hydrogel

Magnetic nanocomposite of temperature responsive hydrogel was used as remote controlled pulsatile drug delivery. Nanocomposites were synthesized by incorporation of superparamagnetic Fe₃O₄ particles in negative temperature sensitive poly (N-isopropyl acrylamide) hydrogels. High frequency alternating magnetic field was applied to produce on demand pulsatile drug release from nanocomposite hydrogel. Hence Nanocomposites hydrogel are one type of On-Off device where drug release can be turn on by application of alternative magnetic field.^[35]

16. Banner's Versetrol Technology

Versetrol Technology is novel innovative technology that provides time controlled release for wide range of drug. In this technology drug is incorporated in lipophilic or hydrophilic matrix and that is than incorporated in soft gelatin capsule shell. This technology is versatile because depending on physiochemical properties of drug either emulsion or suspension can be developed. For lipophilic drugs suspension formulation is preferred while for hydrophilic drugs emulsion form is utilized. By applying combination of lipophilic and hydrophilic matrices desire release profile can be achieved.^[36]

17. Eurand's pulsatile and chrono release System

Eurand's Time controlled pulsatile release system is capable of providing one or more rapid release pulses at predetermined lag times, such as when chronotherapy is required, and at specific sites, such as for absorption along the GI tract^[37]. These capabilities can help optimize

efficacy and/or minimize side-effects of a drug substance.^[38]

18. Three Dimensional Printing (3DP) technology

It is a novel, complex oral dosage delivery system. It is based on solid free-form fabrication method. Complicated internal geometries, varying densities, diffusivities and chemicals are helpful to design such device. Immediate-extended release tablets, pulse release, breakaway tablets and dual pulsatory tablets are examples of complex dosage forms where three dimensional printing technologies have been used. The enteric dual pulsatile tablets were constructed of one continuous enteric excipients phase into which diclofenac sodium was printed into two separated areas. These samples showed two pulses of release in vitro with a lag time between pulses of about 4 h. This technology is the basis of the Their Forms technology. The latter is a micro fabrication process that works in a manner very similar to an "inkjet" 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.^[19]

19. TIMERx technology

It is hydrogel based controlled release device. This technology can provide from zero order to chronotherapeutic release. It can provide different release kinetic by manipulating molecular interactions. The authors claimed that the "molecular engine" replaces the need for complex processing or novel excipients and allows desired drug release profiles to be "factory set" following a simple formulation development process. Basically, this technology 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 TIMERx gum matrix, which expands to form a gel and subsequently releases the active drug substance.^[19]

20. PORT technology

The Programmable Oral Release Technologies (PORT) system is a uniquely coated, encapsulated system that can provide multiple programmed release of drug. It contains a polymeric core coated with a semi permeable, rate-controlling polymer. Poorly soluble drugs can be coated with solubilising agents to ensure uniform controlled release from the dosage form. In capsule form had gelatin capsule is coated with a semipermeable, rate-controlling polymer. Active medicament mixed with osmotic agent is kept inside capsule shell. A water-insoluble plug is used to seal the capsule shell. Immediate release compartment can be added according to need.^[20]

21. Egalet Technology

Developed by Egalet Ltd, Denmark. System consists of an impermeable shell with two lag plugs; active drug is sandwiched between the plugs. After the inert plugs have eroded, the drug is released, thus a lag time occurs. Time of release can be modulated by the length and composition of the plugs. This system shows erosion control drug release. The shells are made of slowly biodegradable polymers (such as ethyl cellulose) and include plasticizers (such as

cetostearyl alcohol), while the matrix of the plugs is made up of a mixture of pharmaceutical excipients including polymers like polyethylene oxide (PEO). Several opioid products are developed using this technology.^[20]

FUTURE SCOPE

Rapid development in the field of drug delivery has led to the formulation of pulsatile drug delivery system, which delivers the drug at right time, place and amount in the patient's body. Circadian rhythm plays important role in the designing of this type of device. Thus designing of proper pulsatile drug delivery will enhance patient compliance, optimum drug delivery to the target site and minimize the undesired effect. Pulsatile drug delivery system provides a unique way of delivering drugs possessing chronopharmacological behavior, extensive first-pass metabolism, a necessity of night time dosing, or absorption window in GIT. Significant modification in the conventional delivery systems in the form of pulsatile delivery system ensures the time controlled pulsatile release of bioactive compounds which is prerequisite for treatment of various disorders like asthma, hypertension, arthritis etc. 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.

CONCLUSION

Although sustained and controlled drug delivery systems have gained a lot of success and application in field of medication, these systems fail to deliver drug according to circadian behaviour of diseases for which pulsatile systems are beneficial. For successful development of chronotherapeutic dosage form, knowledge of circadian time structure, rhythm in disease pathophysiology or 24 hour pattern in symptom intensity of chronic medical conditions and chronopharmacology of medication is needed. Significant progress has been made towards achieving pulsatile drug delivery system that can effectively treat diseases with non-constant dosing therapy.

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