

Recent Technologies for Pulsatile Drug Delivery System

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ABSTRACT

The purpose of writing this review on pulsatile drug delivery systems (PDDS) is to compile the recent literatures with special focus on the different recent technologies involved in the development of the formulation. PDDS are gaining importance in the field of pharmaceutical technology as these systems deliver the right dose at specific time at a specific site thus providing spatial and temporal delivery and increasing patient compliance. These systems are designed according to the circadian rhythm of the body. The principle rationale for the use of pulsatile release of the drugs is where a constant drug release is not desired. A pulse has to be designed in such a way that a complete and rapid drug release is achieved after the lag time. These systems are beneficial for the drugs having chronopharmacological behavior where night time dosing is required, such as anti-arrhythmic and anti-asthmatic. Current review article only discussed the latest technologies to deliver drug in pulsatile fashion.

Keywords: Pulsatile release, Port system, Multiparticulate, SODAS, PORT, PDDS.

1. INTRODUCTION

In recent years considerable attention has been focused on the development of pulsatile drug delivery system. Delivery system with pulsatile release pattern has gained most popular form of controlled drug delivery system because conventional systems with a continuous release are not ideal. Oral controlled drug delivery systems are generally used due to convenient dosage form & it also releases drug in constant or variable rates^{1,2,3}. In these system drug release generally occurs within therapeutic window for prolong period of time. Hence these systems show sustained release of drug from dosage form⁴. There are certain conditions for which constant release pattern i.e. a zero-order release is not suitable and that demand release of a drug after a lag time. In other words, they require pulsatile drug delivery system. Pulsatile drug delivery is time and site-specific drug delivery, thus providing spatial and temporal delivery and increasing patient compliance. These systems are designed according to the circadian rhythm of the body⁴.

Chronobiology is the study of biological rhythms and their mechanisms. There are three types of mechanical rhythms in our body, they are:

- a) Circadian "Circa" means about and "dies" means day.
- b) Ultradian: Oscillation of shorter duration is termed as Ultradian (more than 1 cycle per 24 hrs).

c) Infradian: Oscillations those are longer than 24 h (less than one cycle per day)⁴.

1.1 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^{5,6}.

Oral drug delivery is the most common and convenient for patients, and a reduction in dosing frequency enhances compliance^{7,8}. There are many conditions that demand pulsatile release like¹⁰

- a) Many body functions that follow circadian rhythm. e.g.: Secretion of hormones, acid secretion in stomach, gastric emptying, and gastrointestinal blood transfusion.
- b) Chronopharmacotherapy of diseases which shows circadian rhythms in their pathophysiology like bronchial asthma, myocardial infarction, angina

- pectoris, rheumatic disease, ulcer, and hypertension.
- c) Drugs that produce biological tolerance demand for a system that will prevent their continuous presence at the biophase as this tends to reduce their therapeutic effect.
 - d) The lag time is essential for the drugs that undergo degradation in gastric acidic medium (e.g.: peptide drugs) and irritate the gastric mucosa or induce nausea and vomiting.
 - e) Targeting a drug to distal organs of gastro-intestinal tract (GIT) like the colon requires that the drug release is prevented in the upper two-third portion of the GIT.
 - f) The drugs that undergo first-pass metabolism resulting in reduced bioavailability, altered steady state levels of drug and metabolite, and potential food drug interactions require delayed release of the drug to the extent possible. All of these conditions demand for a time controlled therapeutic scheme releasing the right amount of drug at the right time. This requirement is fulfilled by Pulsatile Drug Delivery Systems^{1, 10}.

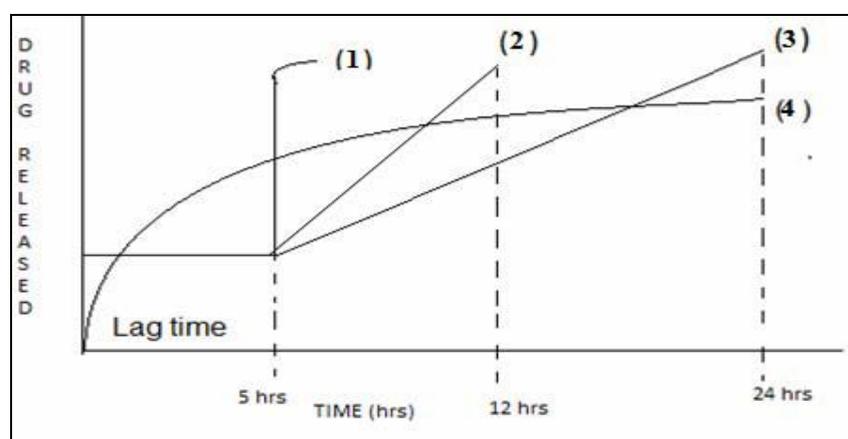


Fig. 1: Schematic representation of different drug delivery systems where 1- sigmoidal release after lag time, 2- delayed release after lag time, 3- sustained release after lag time, 4 - extended release without lag time⁹.

2. RECENT TECHNOLOGIES

2.1 SODAS Technology

A SODA (Spheroidal Oral Drug Absorption System) is Elan's Multiparticulate drug delivery system^[14]. 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^[11]. 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 polymers¹². 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 XR¹³.

2.2 TCES (Time Control Explosion System)

This was described in US Patent no: 4871549. Drug release is caused by explosion

of an insoluble, water permeable membrane. Water permeates the membrane and causes the swelling agent to swell until internal force on membrane causes it to burst there by releasing drug. 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 releases the drug at different time in said environment when the capsule is disintegrated. Each pellet core part contains drug and swelling agent. Core part is surrounded by the water permeable membrane, which prevents the release of the drug into environment. And along with water soluble polymer which solubilizes membrane and increases fragility of membrane as time of contact with water increases. Water

soluble film forming polymer has greater solubility in alkaline pH^{3, 14, 15, 16, 17}.

2.3 IPDAS Technology

The Intestinal Protective Drug Absorption System (IPDAS Technology) is a high density multiparticulate tablet technology, intended for use with GI irritant compounds. IPDAS, Intestinal Protective Drug Absorption System, was initially developed as part of the development process for Elan's proprietary naproxen formulation, Naprelan. The objective was to develop a once daily controlled release system that would have a fast onset of action and reduced gastric irritancy. IPDAS delivery system can also be employed to confer the advantages of multiparticulate technology, in a tablet dosage form. The IPDAS technology is composed of numerous high density controlled release beads, which are compressed into a tablet form^[11]. 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^[13]. 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. The intestinal protection of IPDAS technology is by virtue of the multiparticulate nature of the formulation, which ensures wide dispersion of irritant drug throughout the gastrointestinal tract. Naprelan, which is marketed in the United States and Canada, employs the IPDAS technology. This innovative formulation of naproxen sodium is a unique controlled release formulation indicated both for acute and chronic pain¹³.

2.4 OSDrC Technology

OSDrC means one step dry coating Technology. This 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 creativity⁸.

2.4.1 Advantages of this technology

Accurate & Flexible Control Technology: 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 (API). Misaligned cores are a thing of the past. This paves the way for high value-added drug formulation development, such as divided tablets with two cores, pulsatile tablets with three cores, and combination products. **OSDrC Provides Controlled Release:** Precise OSDrC positioning technology enables product development scientists to control the release of the API by altering the thickness of the outer coating. The ability to precisely position multiple cores allows the creation of tablet products with a variety of pulsatile drug release profiles^{3, 18}.

2.5 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. SkyePharma manufactures several Geomatrix products for its partners, which include Sular for Sciele, ZYFLO CR for Critical Therapeutics, Coruno for Therabel, diclofenac-ratiopharm uno for ratiopharm and Madopar DR for Roche^{4,13}.

2.5.1 Other advantages of the Geomatrix technology are

- Reproducibility
- Efficacy
- Versatility of release control mechanisms
- Controlled release of poorly soluble drugs
- Timed release of drug
- Bi-phasic release of drugs
- Release of 2 or more drugs at different rates
- Pulsed release of drugs
- Safety of use.

2.6 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. Accu-Break Technology is divided in to two types ACCU-B Technology and ACCU-T Technology⁴.

2.7. 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 drug-free 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 capabilities⁴.

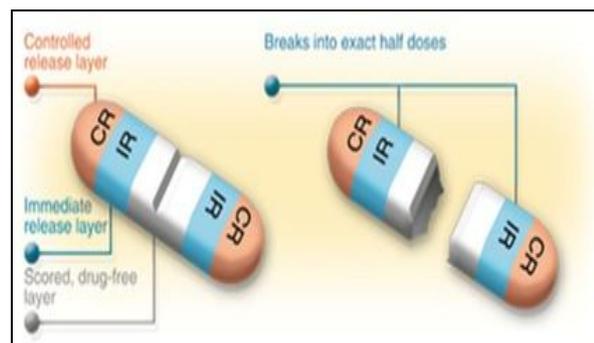


Fig. 2: ACCU-T CR Tri-Layer Tablets⁴

2.8. CODAS Technology

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^[11, 19]. 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^[19, 20, 21].

Advantages of the CODAS technology include a delivery profile designed to complement circadian pattern, controlled onset, an extended release delivery system, rate of release essentially independent of pH, posture and food, "sprinkle" dosing by opening the capsule and sprinkling the contents on food, reduction in effective daily dose and drug exposure, gastrointestinal tract targeting for local effect and reduced systemic exposure to achieve a target profile⁴.

2.9. PRODAS Technology

Programmable Oral Drug Absorption System (PRODAS Technology) is a multiparticulate technology, which is unique in that it combines the benefits of tableting technology within a capsule^{11, 4, 22}.

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. PRODAS technology, by incorporating minitabets with

different release rates, can display the characteristics of a number of different conventional dosage forms:

- Immediate release component will mimic the conventional formulation ensuring that the once daily formulation is as fast acting
- Delayed release can provide site / regional release and food resistance
- Sustained release component provides additional controlled release/protection¹¹.

2.10 TMDS Technology

TMDS (Time Multiple Action Delivery system) 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 time²³.

2.11 DMDS Technology

DMDS (Dividable Multiple Action Delivery System) 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. This allows the patient and physician to adjust the dosing regimen according to the clinical needs without compromising efficacy²⁴.

2.12. PMDS Technology

PMDS (Programmed Multiple-action Delivery System) 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 effects¹³.

2.13 GEOCLOCK Technology

The concept is designed on the basis of Geomatrix technology Skye Pharma developed a new oral drug delivery

technology, Geoclock that allows the preparation of chronotherapy-focused press-coated tablets. 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^{5, 25}. Using this novel technology, SkyePharma has been developing Lodotra, a rheumatoid arthritis drug, on behalf of Nitec Pharma. Lodotra will deliver the active pharmaceutical ingredient at the most suitable time of day to treat the disease²⁵.

2.14 PULSYS Technology

MiddleBrook (Earlier known as Advancis Pharmaceuticals) Pharmaceuticals developed PULSYS, an oral drug delivery technology that enables once daily pulsatile dosing^[19]. 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. PULSYS Technology's Moxatag tablet contain Amoxicillin is designed to deliver amoxicillin at lower dose over a short duration therapy in once daily formulation. Advances have also demonstrated that by preclinical studies which improved bactericidal effect for amoxicillin when deliver in pulsatile manner as compared to standard dosing regimen even against resistant bacteria^{26,27}.

2.15 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-isopropylacrylamide) hydrogels. High frequency alternating magnetic field was applied to produce on demand pulsatile drug release from nanocomposite hydrogel. Nanocomposite hydrogel temperature increase above LCTS so, result in to accelerated collapse of gel. Hence Nanocomposites hydrogel are one type of On-Off device where drug release can be turn on by application of alternative magnetic field²⁸.

2.16 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 physicochemical 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 achieved²⁹.

2.17. 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 tract³⁰. These capabilities can help optimize efficacy and/or minimize side-effects of a drug substance. For example, Eurand has created a circadian rhythm release (CRR) dosage form for a cardiovascular drug, Propranolol hydrochloride, with a four-hour delay in release after oral administration. Administered at bedtime, Propranolol is released after the initial delay such that maximum plasma level occurs in the early morning hours, when the Patient is most at risk. Active core contain drug and non-pareil sugar sphere. Solvent used for preparing core particle and binder to bind drug to the particle, e.g. PVP, HPMC, polysaccharide like dextran, corn starch uses. The drug concentration varies from 10-30% depending on the viscosity of coating formulation. Core may be prepared by granulation, extrusion, spheronization. Then enteric polymer coating layer followed by the water insoluble and enteric polymer mixture. An organic acid containing membrane may be provided between the first and second layer to provide time separated pulse³¹.

2.18. 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 process²⁵.

2.19 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 substance¹³.

2.20 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 need²⁵.

2.21 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 ethylcellulose) 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^{4, 25}.

3. CONCLUSION

Presently, oral delivery of drug is still by far the most preferable route of drug delivery due to the ease of administration, patient compliance and flexibility in its formulations. There are different recent technologies are available for pulsatile drug delivery with different approaches like coating of drug or pellets, tablet within tablet with or without coating, coating with semi permeable, rate controlling polymers to deliver drug in specific amount in specified or required position. PORT technology, TIMERx are such good technology to deliver the drug for pulsatile release. Each technique has its own advantages and disadvantages but depending on our drug and release pattern we can select any technique to formulate pulsatile system from among methods. Thus these techniques help us to deliver controlled or time dependent or site specific delivery of formulation with less frequency and dose of drug. A significant progress has been made toward achieving PDDS that can effectively treat diseases with non-constant dosing therapies. Various pulsatile technologies are researched and some are currently in the market.

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