Recent Techniques For Oral Time Controlled Pulsatile Technology
B Prajapati, H Solanki

Abstract
Pulsatile drug delivery system is defined as the rapid and transient release of certain amount of drug molecules within a short time period immediately after a predetermined off-release period, i.e., lag time. Pulsatile drug delivery aims to release drug on programmed pattern i.e. at appropriate time and at appropriate site of action. Pulsatile systems are gaining a lot of interest as the drug is released completely after defined lag time. Pulsatile drug delivery system is time- and site-specific drug delivery system, thus providing special and temporal delivery and increasing patient compliance.

INTRODUCTION
Pulsatile drug delivery system is defined as the rapid and transient release of certain amount of drug molecules within a short time period immediately after a predetermined off-release period, i.e., lag time. [1] Pulsatile drug delivery aims to release drug on programmed pattern i.e. at appropriate time and at appropriate site of action. Pulsatile systems are gaining a lot of interest as the drug is released completely after defined lag time. Pulsatile drug delivery system is time- and site-specific drug delivery system, thus providing special and temporal delivery and increasing patient compliance. [1, 2] In recent pharmaceutical applications involving pulsatile delivery, multiparticulate dosage forms are gaining much favor over single-unit dosage forms. [3] Currently pharmaceutical company focused on developing and commercializing pulsatile drug products that fulfill unmet medical needs in the treatment of various diseases. [4]

1. 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™ Technology. [6]

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 capabilities. [6]

Figure 1
Figure 1 : ACCU-T CR Tri-Layer Tablets [6]

2. SODAS® TECHNOLOGY
SODAS® (Spheroidal Oral Drug Absorption System) is Elan’s Multiparticulate drug delivery system. 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. [7]

Elan can provide a number of tailored drug release profiles, including immediate release of drug followed by sustained release to give rise to a fast onset of action, which is maintained for 24 hours. Alternatively the opposite scenario can be achieved where drug release is delayed for a number of hours. An additional option is pulsatile release, where a once daily dosage form can resemble multiple daily doses by releasing drug in discrete bursts throughout the day.

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. [8]

The most recent regulatory approvals for a SODAS® based system occurring with the launch of once-daily oral dosage forms of Avinza™, Ritalin® LA and Focalin® XR. [5]

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. [7]

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. [5] Release of active ingredient from the multiparticulates occurs through a process of diffusion either through the polymeric membrane and or the micromatrix 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 pain. [5]

4. 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. [3, 7]

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. [5, 9]

CODAS™ PRODUCT DEVELOPMENT
Elan’s Verelan® PM represents a commercialized product using the CODAS™ technology. The Verelan® PM formulation was designed to begin releasing Verapamil
approximately four to five hours post ingestion. This delay is introduced by the level of release-controlling polymer applied to the drug-loaded beads. (4) The release-controlling polymer is a combination of water-soluble and water-insoluble polymers. As water from the gastrointestinal tract contacts the polymer coat beads, the water-soluble polymer slowly dissolves, and the drug diffuses through the resulting pores in the coating. The water-insoluble polymer continues to act as a barrier, maintaining the controlled-release of the drug. When taken at bedtime, this controlled onset extended release delivery system enables a maximum plasma concentration of Verapamil in the morning hours, when blood pressure normally rises from its overnight low. [4, 5, 9]

5. PRODAS® TECHNOLOGY

Programmable Oral Drug Absorption System (PRODAS® Technology) is a multiparticulate technology, which is unique in that it combines the benefits of tabletting technology within a capsule. [7]

The PRODAS® delivery system is presented as a number of minitablets 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 minitablets, each one formulated individually and programmed to release drug at different sites within the gastro-intestinal tract. It is also possible to incorporate minitablets of different sizes so that high drug loading is possible.

PRODAS® technology, by incorporating minitablets with different release rates, can display the characteristics of a number of different conventional dosage forms:

Immedicate 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/ protection. [5, 7]

6. TMDS TECHNOLOGY

TMDS (Time Multiple Action Delivery system) Technology provide control release rate of multiple ingredient within single tablet in programme manner. TMDS Technology allows for more than one active ingredient in a single tablet formulation provide multiple release profile over extended period of time. [10, 11]

7. 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 efficacy. [10, 12]

8. 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 effects. [10]

9. GEOCLOCK® TECHNOLOGY

SkyePharma 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. [13]

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.
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 disease. [13]

10. GEOMATRIX™ TECHNOLOGY
The Geomatrix™ technology is applied to achieve customised 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 methycellulose (HPMC) and 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. [13]

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. [13]

11. PULSYS™ TECHNOLOGY
MiddleBrook™ (Earlier known as Advancis Pharmaceuticals) Pharmaceuticals developed PULSYS™, an oral drug delivery technology that enables once daily pulsatile dosing. [3] 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. Advancis 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. [3, 14, 15, 23]

12. 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 are “unique”, “High quality”, “low cost” and “Innovative” [16]

The OSDrC® rotary tabletting 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. [16,17]

ADVANTAGES OF THIS TECHNOLOGY
1. 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.

2. POOR-COMPRESSIBILITY ENCASING TECHNOLOGY
OSDrC® technology allows incorporation of core ingredients with poor compressibility, such as magnesium stearate. OSDrC® tablets with pellets as their core can replace conventional capsules. OSDrC® paves the way for development of various novel drug formulations, such as new oral rapid disintegration tablets.

3. OSDRC® PROVIDES CONTROLLED...
**REVIEW**

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. [16, 17]

**13. INTELLIMATRIX™ TECHNOLOGY**

IntelliPharmaceutical is a pharmaceutical technology development company with a suite of proprietary tablet technologies. This Company have developed Novel oral Time controlled Release Matrix tablet Known as IntelliMatrix™ tablet. IntelliMatrix™ drug delivery platform is unique composition of several different ‘intelligent’ polymers such as hydroxy ethylcellulose and a channel former as Lactose. IntelliMatrix™ system is at the heart of proprietary drug delivery. Proprietary modelling enables precise profile control and site specific drug delivery. [18]

**14. 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. [21] 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. [19, 20]

**15. EURAND’S DIFFUCAPS® MULTIPARTICULATE SYSTEM**

Diffucaps® multiparticulate system customized drug release profiles are created by first layering active drug onto an inert core (such as a sugar/cellulose sphere), then applying one or more rate-controlling, functional polymers, to produce spherical, multi-layered particles.[20,22] Eurand’s Innopran® XL tablet represents commercialized product of Diffucap® multiparticulate system. The Innopran® XL formulation was designed to begin releasing of Propranolol and Verapamil approximately four to five hours post ingestion. This delay is introduced by the level of release-controlling polymer applied to the drug-loaded beads. [3, 7, 20]

**16. DIFFUTAB® TECHNOLOGY**

Diffutab® technology for sustained release profiles and targeted delivery of pharmaceutical products. This technology incorporates a blend of hydrophilic polymers that control drug release via diffusion through, and erosion of, a matrix tablet. The Diffutab technology is particularly useful for the development of high dosage products and is an effective way to develop sustained release, once-a-day dosage forms. [20]

**17. ORBEXA® TECHNOLOGY**

Orbexa® technology is a multiparticulate system that enables high drug loading and provides a formulation choice for products that require granulation. This technology produces beads that are of controlled size and density - and suitable for formulation as controlled release multiparticulates - using granulation, spheronization and extrusion techniques. The resultant beads can be coated with functional polymer membranes for additional release rate control and may be filled into capsules or provided in sachet form. This process allows for high drug concentrations within each bead. The technology is suited for use with sensitive drugs such as proteins. [19, 20]

**18. EURAND MINITABS® TECHNOLOGY**

Eurand Minitabs® technology combines the simplicity of tablet formulation with the sophisticated drug release control offered by multiparticulate drug forms. Eurand Minitabs are tiny, approximately 2 mm in diameter, cylindrical tablets. Functional membranes may be applied to the tablets to further control release rate. Eurand Minitabs offer high drug loading, a wide range of release rate designs, and fine tuning of these release rates. Capsules containing the Eurand Minitabs can be opened and the contents used as a “sprinkle” formulation. [20]

**19. BANNER’S VERSETROLTM TECHNOLOGY**

VerstroITM 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. [24, 25]

20. MAGNETIC NANOCOMPOSITE HYDROGEL

Magnetic nanocomposite of temperature responsive hydrogel was used as remote controlled pulsatile drug delivery. Nanocomposites were synthesized by incorporation of superparamagnetic Fe$_3$O$_4$ 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 field. [26]

References

Author Information

Bhupendra. G. Prajapati
S.K. Patel College of Pharmaceutical Education & Research, Ganpat Vidyanagar, Ganpat University, Kherva. PIN: 382711, Mehsana, Gujarat, India.

Himanshu Solanki
S.K. Patel College of Pharmaceutical Education & Research, Ganpat Vidyanagar, Ganpat University, Kherva. PIN: 382711, Mehsana, Gujarat, India.