Review Article

# Pulsatile Delivery Systems: An Approach for Chronotherapeutic Diseases

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ARTICLE INFO

*Article history:*
Received 28 August 2009
Accepted 18 September 2009
Available online 04 February 2010

*Keywords:*
Circadian rhythm
Lag time
Multiple-unit system
Pulsatile release
Pulsincap

**DOI:** 10.4103/0975-8453.59513

ABSTRACT

Delivery systems with a pulsatile release pattern are receiving a sprouting attraction for the development of drugs for which conventional controlled-release systems with a continuous release are not ideal. Most physiological, biochemical, and molecular processes in healthy organisms display robust, predictable changes on a 24-h schedule. Chronotherapeutic products can synchronize drug delivery with circadian rhythms in order to optimize efficacy and/or minimize side effects. These products follow a sigmoidal release profile characterized by a time period of no release (lag time) followed by a rapid and complete drug release. Various capsular, osmotic, single and multiple unit systems are based on the use of soluble/erodible polymer coatings, rupturable membranes, and membrane permeabilities. Marketed technologies such as PULSYS™, CODAS®, TIMERx®, and DIFFUCAPS® follow one of the above mechanisms to render a sigmoidal drug release profile. So these systems are tuned according to body's circadian clock having a potential to improve quality of patients life undergoing conventional drug therapy.

## Introduction

Oral drug delivery is the largest and the oldest segment of the total drug delivery market. It is the fastest growing and most preferred route for drug administration.[1] For many disease states the ideal dosage regimen is that by which an acceptable therapeutic concentration of drug at the site (s) of action is attainted immediately and is then maintained constant for the desired span of the treatment.[2] Over the past three decades, advancements in research aiming toward underlying principles to bring both commercial and therapeutic values to health care products are contributing to novel drug delivery systems.[3] Marketing new drug entities have increased, with concomitant recognition of the therapeutic advantages of modified release per conventional oral dosage forms; greater attention has been focused on the development of sustained, controlled, and delayed release system.[4] These new and/or improved delivery systems work on various principles by providing variable/constant drug mounts over a particular time period in our body based on the fact that physiologic parameters display constancy over a time.[3]

Recent studies have revealed that diseases have a predictable cyclic rhythm and that the timing of medication regimens can improve the outcome of a desired effect.[5] This condition demands release of drug as a "pulse" after a lag time and has to be designed in such a way that a complete and rapid drug release should follow the lag. Such systems are called as pulsatile drug delivery systems (PDDS), time-controlled systems, or sigmoidal release systems as shown in Figure 1.

The need for such a novel sigmoidal drug delivery pattern has been hunt for the following.

a) Chronopharmacotherapy of diseases governed by the master circadian clock of the body
b) Refrain gastric soreness or drug instability in acidic pH
c) Drugs, such as β-blockers or β-estradiol, undergoing extensive first pass metabolism

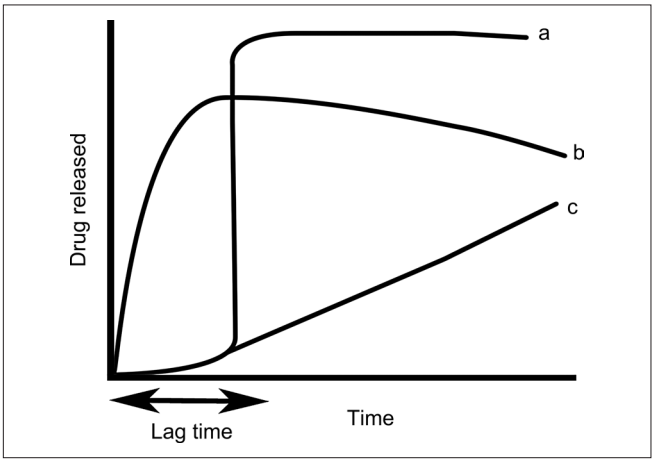


**Figure 1:** Drug release profiles. (a) Sigmoidal release; (b) extended release; (c) extended release after lag time

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d) Colon targeting of drugs for localized diseases such as ulcerative colitis, Crohn's disease and enhance delivery of proteins and peptides

## Chronopharmacotherapy

Humans exhibit endogenous circadian rhythms that are regulated by the master circadian clock of the body, the suprachiasmatic nucleus.[6] Humans possess many biological clocks, depending on the cycle it could be an infradian (longer than a day), ultradian (shorter than a day), circadian (about a day), or circannual (about a year) rhythm.[7] The term chronopharmacotherapy can be split into chronopharmacology and chronokinetics. Chronopharmacology involves the study of the effects of drugs as a function of biological timing and on the characteristics of rhythms. Chronokinetics refers to rhythmic changes in bioavailability, absorption, distribution, metabolism and excretion of drug.[8]

The diseases currently on target for chronopharmaceutical formulations are those for which there are enough scientific background to justify chronopharmaceutical drug delivery system, compared to conventional drug administration approach. The diseases are

*Asthma*: Asthma is one of the most studied diseases for its chronobiological behavior. Circadian changes in the physiology of the lungs of asthmatic patients results in an increase in diurnal resistance causing dyspnea. Nocturnal asthma symptoms are precipitated in early morning between 3.0 am and 5.0 am.[8-10]

*Allergic rhinitis*: Symptoms of sneezing, runny nose, and stuffy nose are typically worse in the early waking hours than later during the day (nasal inflammation associated with hay fever).[9]

*Rheumatoid arthritis:* Rheumatoid arthritis (RA) varies within a day and between days in a circadian manner and the daily morning stiffness that is observed in RA patients has become one of the diagnostic criteria of the disease.[11] Human pro-inflammatory cytokine production exhibits a diurnal rhythmicity with peak levels during the night and early morning, at a time when plasma cortisol (anti-inflammatory) is lowest and melatonin (pro-inflammatory) is highest.[12]

*Osteoarthritis:* Symptoms of osteoarthritis worsen in the afternoon and evening.[9]

*Ulcers:* Maximal acid secretion, peptic ulcer disease pain, and perforation of gastric and duodenal ulcers are more common at night.[13,14]

*Myocardial Infarction:* The onset of myocardial infarction has been shown to be more frequent in the morning with ~35% events occurring between 6 am and noon. Acute cardiac arrest and transient myocardial ischemia show an increased frequency in morning. The causes for these findings have been suggested to be release of catecholamines, cortisol, increase in the platelet aggregation and vascular tone.[13]

*Hypercholesterolemia:* Circadian rhythm of cholesterol biosynthesis states higher rates of cholesterol intake and hepatic cholesterogenesis occurring during the evening hours.[13]

## 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.

### *Single-unit pulsatile systems*

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

### *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 R. P. 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 2] and slowly pulled itself out of capsule at a controlled rate independent of nature and pH of the medium giving a rapid bulk release.[15]

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 (HPMC), polyvinyl alcohol, polyethylene oxide), congealed melted polymers (e.g., saturated polyglycolated glycerides, glyceryl monooleate), and enzymatically controlled erodible polymer (e.g., pectin).[16,17] The technology was first commercialized in 1997 under trade name SprintSalmonella™ by Oxoid Ltd, Basingstoke, UK.[18] Ross *et al*.[19] used low substituted hydroxypropylcellulose (HPC) in the expulsion system for the release of propranolol over a time period of 2-10h. This lag could be controlled using compressed erodible tablets made of lactose and HPMC. Krogel and Bodmeier[16] 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 al*.[20] designed a hydrophilic sandwich capsule based on a system where the capsule was enclosed

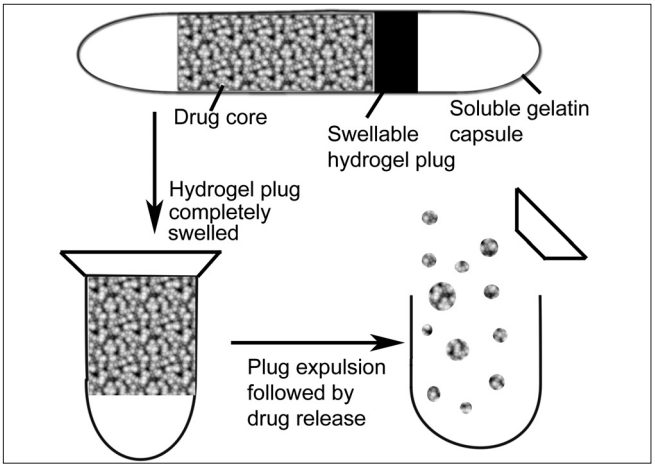


**Figure 2:** Pulsincap system

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.

*Capsular system based on osmosis*

The basic appliance in the osmotic system is a capsule enclosed with a semipermeable membrane. Inside the capsule 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 time.[21]

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 3]. 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 non-swellable 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 solublization of the osmotically active agent. The hydrostatic pressure developed pushes the non-swellable plug out as the drug is release 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 separators.[22] Crison *et al*. proposed such system to deliver methylphenidate for the treatment of attention deficit hyperactivity disorder in school age children.[23,24]

*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 solublization, dispersion, and protection from enzymatic degradation.[25]

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 4. 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®.[26-28]

*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 5. The lag time needed for pulsatile delivery is achieved by a series of stops placed along the inner wall of capsule which

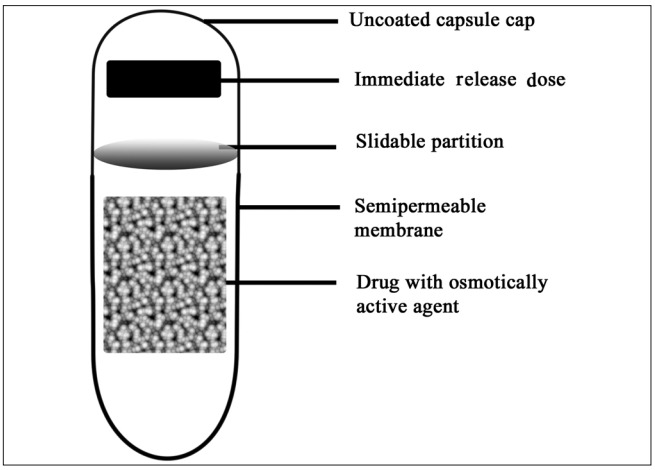


**Figure 3:** The PORT system

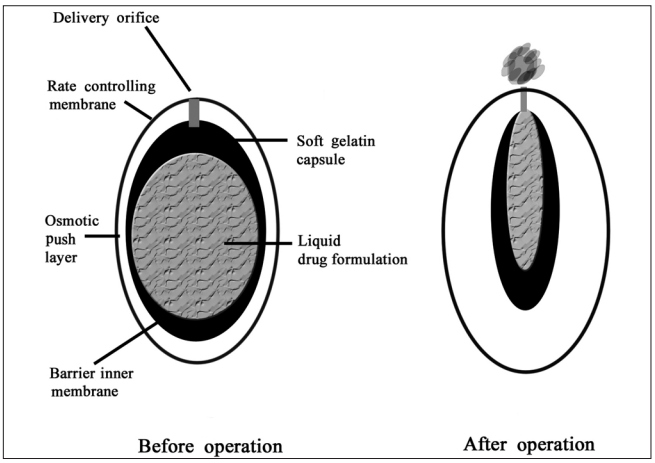


**Figure 4:** L-OROS Softcap system

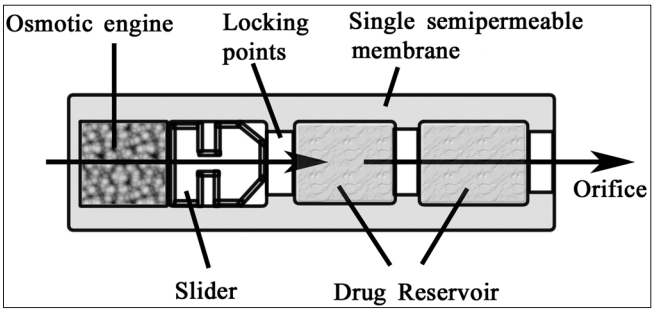


**Figure 5:** Pulsatile delivery by series of stops

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 axis.[29]

## *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 6]. 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 release.[30-32]

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 HPMC.[33] 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, as described in US Patent 4865849. 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 dissolved.[34,35]

*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.

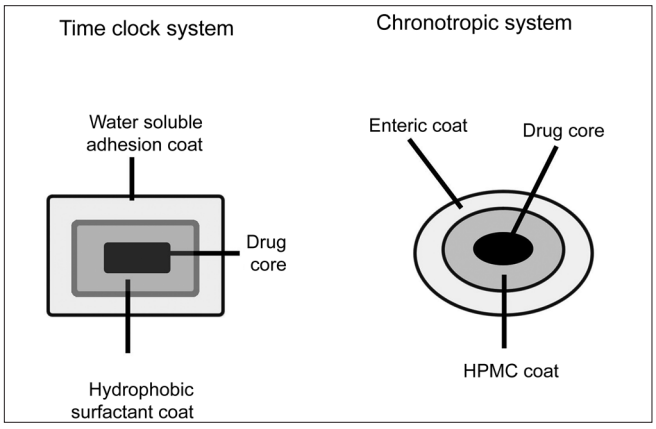


**Figure 6:** Time clock and chronotropic systems

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 time.[36]

## *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.

## *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.[37,38]

Ueda *et al*.[39-42] developed a time-controlled explosion systems (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 disintegrants. 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.

*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*.[43] 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 fiuids 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

**Table I: List of marketed pulsatile release systems[52-55]**

| Technology | Mechanism | Proprietory name and dosage form | API | Disease |
|---|---|---|---|---|
| CODAS® | Multiparticulate pH dependent system | Verelan® PM; XL release capsule | Verapamil HCl | Hypertension |
| OROS® | Osmotically regulated | Covera-HS®; XL tablet | Verapamil HCl | Hypertension |
| DIFFUCAPS® | Multiparticulate system | Innopran®; XL tablets | Verapamil HCl Propranolol HCl | Hypertension |
| Pulsincap™ | Rupturable system | PulsincapTM | Dofetilide | Hypertension |
| PULSYS™ | Multiparticulate system | Moxatag™ tablet | Amoxicillin | Infection |
| TIMERx® | erodible/soluble barrier coating | OPANA® ER tablet | oxymorphone | Pain managment |
| Covera-HS® | Osmotically regulated | Covera-HS® ER tablets | Verapamil HCl | Hypertension |
| Procardia XL® | Osmotically regulated | Procardia XL SR | Nifedipine | High blood pressure and Angina |

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 microparticulates.[44]

*Systems with changed membrane permeability*

The release profile in this system depends on physic-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.*[45,46] 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 membrane.[47-49]

## Marketed technologies

The marketed technologies of pulsatile delivery systems are listed in Table 1. CODAS® (Chronotherapeutic Oral Drug Absorption System) is one of Elan Drug Technologies, multiparticulate drug delivery systems. The CODAS® technology is designed to allow a 4-5 h delay for onset following administration of drug. This delay in release is introduced by the level of release-a controlling polymer applied to the drug-loaded beads. Applying the CODAS® technology to Verapamil Hydrochloride, Verelan® PM complimented the circadian pattern of hypertension and helped to minimize the risk of early morning cardiovascular events.[50] Penwest Pharmaceuticals and Co., USA, considered to be top runner in drug delivery technologies with patented products such as TIMERx®, Geminex® and SyncroDose™ The TIMERx oral drug delivery system achieves a variety of release profiles (First order, Zero order, BurstCR, etc.) for a wide range of drugs, accommodating even the most difficult actives. TIMERx enabled Penwest to meet the significant challenges of today's pharmaceutical marketplace head-on with 32 US issued patents and 178 patents worldwide.[51] Alza Corporation uses OROS (Osmotic Release Oral Systems) drug delivery platform with marketed products such as Covera-HS® and Procardia XL®. Eurand Pharmaceuticals DIFFUCAPS® technology is a multiparticulate system that provides optimal release profiles for either single drugs or for a combination of drugs.[37]

## Future prospects

The development of chronotherapeutic, pulsatile-release products is most challenging as to get the right drug to the right place at the right time. Multiparticulates offer more advantages in respect to dose dumping and transit time variability when compared with single-unit pulsatile systems. The novel PDDS pays more attention on site and time-specific drug delivery. In these systems, there is release of the drug after stimulation by any biological factor such as temperature, or any other chemical stimuli. In the case of diabetes mellitus, there is a rhythmic increase in the levels of glucose in the body requiring injection of the insulin at proper time. Glucose-responsive insulin release devices based on stimulus produced by pH sensitive hydrogel will be a great boon to diabetics in future. Externally regulated systems are also explored using stimuli produced by magnetism, ultrasound, electrical effect, and irradiation.

## Conclusion

Oral drug delivery is the largest, oldest, and most preferred route of drug delivery. Universally sustained and controlled-release products provide a desired therapeutic effect, but fall for diseases following biological rhythms. Circadian disorders such as asthma, osteoarthritis, RA, cholesterol synthesis, etc., require chronopharmacotherapy. Pulsatile drug delivery can effectively crack this problem as it is modulated according to body's circadian clock giving release of drug after a specified lag time. During the last two decades, technologies to ensure time-controlled pulsatile release of bioactive compounds have been developed. 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 brought in the market, which surely assure a bright and promising future.

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Source of Support: Nil, **Conflict of Interest:** None declared.