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 types and approaches 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. Some of the disease conditions wherein PDDS are promising include duodenal ulcer, cardiovascular diseases, arthritis, asthma, diabetes, neurological disorder, cancer, hypertension and hypercholesterolemia. PDDS can be classified into time controlled systems wherein the drug release is controlled primarily by the delivery system, stimuli induced PDDS in which release is controlled by the stimuli, such as the pH or enzymes present in the intestinal tract or enzymes present in the drug delivery system and externally regulated system where release is programmed by external stimuli like magnetism, ultrasound, electrical effect and irradiation. This review also summarizes some current PDDS already available in the market. These systems are useful to several problems encountered during the development of a pharmaceutical dosage form.

Keywords: Pulsatile drug delivery systems; Circadian rhythm; Single unit, Multiple units, Pulsatile release pulsincap

Introduction

Controlled drug delivery systems have acquired very important role in pharmaceutical Research and Development (R&D) business. Such systems offer control over the release of drug and grant a new lease on life to a drug molecule in terms of patentability. These dosage forms offer many advantages over the conventional drug delivery systems; such advantages include nearly constant drug level at the site of action, prevention of peak-valley fluctuations, reduction in dose of drug, reduced dosage frequency, avoidance of side effects, and improved patient compliance [1]. The oral controlled-release system shows a typical pattern of drug release in which the drug concentration is maintained in the therapeutic window for a prolonged period of time, thereby ensuring sustained therapeutic action.

However, there are certain conditions for which such a release pattern is not suitable. These conditions demand release of drug after a lag time. In other words, it is required that the drug should not be released at all during the initial phase of dosage form administration. Such a release pattern is known as pulsatile release [2]. 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 [2]. This condition demands release of drug as a "pulse" after a time lag and such system has to be designed in a way that complete and rapid drug release should follow the lag time. Such systems are known as pulsatile drug delivery systems (PDDS), time-controlled systems, or sigmoidal release systems (Fig 1). PDDS have been developed in close connection with emerging chronotherapeutic views. In this respect, it is well established that the symptoms of many pathologies, as well as the pharmacokinetic and pharmacodynamic profiles of most drugs, are subject to circadian variation patterns.

Figure 1. Schematic representation of different drug delivery systems where (a)= sigmoidal release after lag time, (b)= delayed release after lag time, (c) = sustained release after lag time, (d) = extended release without lag time.

As far as widespread chronic pathologies with night or early morning symptoms are concerned, such as cardiovascular disease (CVD), bronchial asthma and rheumatoid arthritis, remarkable efficacy, tolerability and compliance benefits could arise from modified release medications. After bedtime administration, would allow the onset of therapeutic drug concentrations to coincide with the time at which disease manifestations are more likely to occur. Performance of pulsatile delivery fulfills such goals.

In addition to being potentially suitable for chronotherapy, pulsatile release is also exploited to target proximal as well as distal colonic regions via the oral route. Colon delivery is being extensively investigated as it may yield improved topical inflammatory bowel disease (IBD) treatments and is even suggested as one means of enhancing the poor oral bioavailability of peptides, proteins, oligonucleotides and nucleic acids. For the purpose of time-controlled colon targeting, delayed-release systems have to be presented in an enteric-coated configuration so that the high intra- and inter-subject variability in gastric residence may be overcome, and provide, following stomach emptying, a lag phase roughly corresponding to fairly reproducible small intestinal transit time [3].

Diseases targeted for pulsatile technology
Diseases presently targeted for chronopharmaceutical formulations are those for which there are enough scientific backgrounds to justify PDDS- compared to the conventional drug administration approach. They include: hypercholesterolemia, asthma, cancer, duodenal ulcer, arthritis, diabetes, neurological disorders, cardiovascular diseases (e.g. hypertension and acute myocardial infarction) and colonic delivery. The rationale for chronotherapy/pulsatile release for each of these diseases will be briefly reviewed below [4-7].

i. Hypercholesterolemia
Diverse directions of circadian changes in lipid fractions in patients and normal subjects may contribute to alteration in the rhythmicity of other metabolisms and in the blood coagulation system, thus leading to various complications [8]. A circadian rhythm occurs during hepatic cholesterol synthesis [9, 10]. Therefore, cholesterol synthesis is generally higher during the night than during daylight. The maximal production occurs early in the morning, i.e. 12 h after the last meal [11]. Studies with HMG CoA reductase inhibitors have suggested that evening dosing was more effective than morning dosing [12, 13].

ii. Asthma
The chronotherapy of asthma has been extensively studied. The role of circadian rhythms in the pathogenesis and treatment of asthma indicates that airway resistance increases progressively at night in asthmatic patients [14]. Circadian changes are seen in normal lung function, which reaches a low point in the early morning hours. As broncho constriction and exacerbation of symptoms vary in a circadian fashion,
asthma is well suited for chronotherapy. Chronotherapies have been studied for asthma with oral corticosteroids, theophylline, and B2-agonists [15, 16].

iii. Cancer
Human and animal studies suggest that chemotherapy may be more effective and less toxic if cancer drugs are administered at carefully selected times that take advantage of tumor cell cycles while less toxic to normal tissue [17, 18]. The blood flow to tumors was threefold greater during each daily activity phase of the circadian cycle than during the daily rest phase [19]. The chronotherapy concept offers further promise for improving current cancer-treatment options, as well as for optimizing the development of new anticancer or supportive agents [20].

iv. Duodenal ulcer
Many of the functions of the gastrointestinal tract are subject to circadian rhythms: gastric acid secretion is highest at night [21, 22], while gastric and small bowel motility and gastric emptying are all slower at night. During night time, when gastric motility and emptying are slower, drug disintegration, dissolution, and absorption may be slower [23]. In peptic ulcer patients, gastric acid secretion is highest during the night. Suppression of nocturnal acid is an important factor in duodenal ulcer healing. Therefore, for active duodenal ulcer, once daily at bedtime is the recommended dosage regimen for an H2 antagonist [24].

v. Arthritis
The chronobiology, chronopharmacology and chronotherapeutics of pain have been extensively reviewed [25]. For instance, there is a circadian rhythm in the plasma concentration of C-reactive protein [26] and interleukin-6 [27] of patients with rheumatoid arthritis. Patients with osteoarthritis tend to have less pain in the morning and more at night; while those with rheumatoid arthritis, have pain that usually peaks in the morning and decreases throughout the day. Chronotherapy for all forms of arthritis using NSAIDs such as Ibuprofen should be timed to ensure that the highest blood levels of the drug coincide with peak pain.

vi. Diabetes
The circadian variations of glucose and insulin in diabetes have been extensively studied and their clinical importance in case of insulin substitution in type I diabetes have been previously discussed [28, 29]. The goal of insulin therapy is to mimic the normal physiologic pattern of endogenous insulin secretion in healthy individuals, with continuous basal secretion as well as meal-stimulated secretion.

vii. Neurological disorders
As an integrative discipline in physiology and medical research, chronobiology renders the discovery of new regulation processes regarding the central mechanisms of epilepsy. Chronophysiology investigations considered at a rhythmometric level of resolution suggest several heuristic perspectives regarding (i), the central pathophysiology of epilepsy and (ii) the behavioural classification of convulsive events [30].

viii. Cardiovascular diseases
Several functions such as. Blood pressure (BP), heart rate, stroke volume, cardiac output, blood flow of the cardiovascular system are subject to circadian rhythms. For instance, capillary resistance and vascular reactivity are higher in the morning and decrease later in the day. Platelet aggregability is increased and fibrinolytic activity is decreased in the morning, leading to a state of relative hypercoagulability of the blood [31, 32]. It was postulated that modification of these circadian triggers by pharmacologic agents may lead to the prevention of adverse cardiac events [33]. BP is at its lowest during the sleeping period and rises steeply during the early morning period. Most patients with essential hypertension have a similar circadian rhythm of BP as do normotensive persons, although hypertensive patients have an upward shift in the profile [34].

ix. Colonic delivery
The colon is also seen as the preferedabsorption site for oral administration of protein and peptide drugs, because of the relatively low proteolytic enzyme activities in the colon. A colon-specific drug delivery system should prevent drug release in the stomach and small intestine, and affect an abrupt onset of drug release upon entry into the colon. Time dependent
delivery has also been proposed as a means of targeting the colon. Time-dependent systems release their drug load after a pre-programmed time delay. To attain colonic release, the lag time should equate to the time taken for the system to reach the colon. This time is difficult to predict in advance, although a time lag of five hours is usually considered sufficient, given that small intestinal transit time is reported to be relatively constant at three to four hours [35]. All of these conditions demand a time-programmed therapeutic scheme releasing the correct amount of dose of the drug at the appropriate time. This requirement is usually fulfilled by PDDS.

Methodologies for PDDS
Methodologies for the PDDS can be broadly classified into four classes;

I. Time controlled pulsatile release
   A. Single unit system
   B. Multi-particulate system
II. Stimuli induced
   A. Thermo-Responsive Pulsatile release
   B. Chemical stimuli induced Pulsatile systems
III. External stimuli pulsatile release
   A. Electro responsive pulsatile release
   B. Magnetically induced pulsatile release
IV. Pulsatile release systems for vaccine and hormone products

I. Time controlled pulsatile release system
These time-controlled systems can be classified as single unit (e.g., tablet or capsule) or multiple unit systems.

1. Single unit systems
i. Capsular Systems
Different single-unit capsular PDDS have been developed (Fig 2). A general design of such systems consists of an insoluble capsule body housing a drug and a plug. The plug is removed after a predetermined time lag due to swelling, erosion, or dissolution. The Pulsincap® system is an example of such a system that is made up of a water-insoluble capsule body filled with drug formulation [36]. The body is closed at the open end with a swellable hydrogel plug. Upon contact with dissolution medium or gastro-intestinal fluids, the plug swells, pushing itself out of the capsule after a time lag. This is followed by a spontaneous release of the drug (Fig 2). The time lag can be controlled by manipulating the dimension and the position of the plug. For water insoluble drugs, a spontaneous release can be ensured by inclusion of effervescent agents or disintegrants. The plug material consists of insoluble but permeable and swellable polymers (e.g.:polymethacrylates) [37,38], erodible compressed polymers (e.g: hydroxypropylmethyl cellulose, polyvinyl alcohol, polyethylene oxide), congealed melted polymers (e.g: saturated polyglycolated glycerides, glycerylmonooole and enzymatically controlled erodible polymer e.g:pectin). These formulations are well tolerated in animals and healthy volunteers, and there have been no reports of gastro-intestinal irritation. However, there was a potential problem of variable gastric residence time, which was overcome by enteric coating the system to allow its dissolution only in the higher pH region of small intestine.

ii. Port systems
The Port System - consists of a gelatin capsule coated with a semi permeable membrane (e.g: cellulose acetate) housing an insoluble plug (e.g: lipicid) and an osmotically active agent along with the drug formulation [39]. When it comes in contact with the aqueous medium, water diffuses across the semi permeable membrane, resulting in increased inner pressure that ejects the plug after a – time lag. The time lag is controlled by the thickness of semi permeable membrane. The system showed good correlation in lag times of in-vitro and in-vivo experiments in humans [40]. In order to deliver drug in liquid form, an osmotically driven capsular system was developed. In this system, liquid drug is absorbed into highly porous particles, which release the drug through an orifice of a semi permeable capsule supported by an expanding osmotic layer after the barrier layer is dissolved [41]. The capsular system delivers drug by the capsule's osmotic infusion of moisture from the body. The capsule wall is made up of an elastic material and possesses an orifice. As the osmosis proceeds, the pressure within the capsule rises, causing the wall to stretch. The orifice is small enough so that when the elastic wall relaxes, the flow of the drug through the orifice essentially stops, but when the elastic wall is
distended beyond threshold value, the orifice expands sufficiently to allow drug release at a required rate. Elastomers, such as styrene-butadiene copolymer have been suggested [42, 43].

iii. Delivery by a series of stops
This system is described for implantable capsules. The capsule contains a drug and a water-absorptive osmotic engine that are placed in compartments separated by a movable partition. The pulsatile delivery is achieved by a series of stops along the inner wall of the capsule. These stops obstruct the movement of the partition but are overcome in succession as the osmotic pressure rises above a threshold level. The number of stops and the longitudinal placements of the stops along the length of the capsule dictate the number and frequency of the pulses, and the configuration of the partition controls the pulse intensity. This system was used to deliver porcine somatotropin [44].

iv. Delivery by solubility modulation
These systems contain a solubility modulator for pulsed delivery of variety of drugs. The system was especially developed for delivery of salbutamol sulphate [45]. The compositions contain the drug (salbutamol sulphate) and a modulating agent, sodium chloride (NaCl). The amount of NaCl was such that it was less than the amount needed to maintain saturation in a fluid that enters the osmotic device. The pulsed delivery is based on drug solubility. Salbutamol has solubility of 275 mg/ml in water and 16 mg/ml in saturated solution of NaCl, while NaCl has solubility of 321 mg/ml in water, and its saturation solubility is 320 mg/ml. These values show that the solubility of the drug is a function of the modulator concentration, while the modulators solubility is largely independent of drug concentration. The modulating agent can be a solid organic acid, inorganic salt, or organic salt.

v. Delivery by reservoir systems with erodible or soluble barrier coatings
Most of the pulsatile drug delivery systems are reservoir devices coated with a barrier layer. This
barrier erodes or dissolves after a specific lag period, and the drug is subsequently released rapidly. The time lag depends on the thickness of the coating layer [46].

The Time Clock® system consists of a solid dosage form coated with lipid barriers containing carnauba wax and beeswax along with surfactants, such as polyoxyethylene sorbitan monooleate [47, 48]. This coat erodes or emulsifies in the aqueous environment in a time proportional to the thickness of the film, and the core is then available for dispersion. The major advantage of this system is its ease of manufacture without any need of special equipment. The disadvantage of this system is a premature drug release when the penetrating water dissolves the drug.

The Chronotropic® system consists of a drug-containing core coated by hydrophilic swellable hydroxypropylmethyl cellulose (HPMC), which is responsible for a lag phase in the onset of drug release [49]. Time lag is controlled by the thickness and the viscosity grades of HPMC used in coating the drug core. The system is suitable for both tablets and capsule formulations [50].

2. Multiparticulate Systems

Multi-particulate drug delivery systems are mainly oral dosage forms consisting of a multiplicity of small discrete units, in which the active substance is present as a number of small independent subunits. They provide many advantages over single-unit systems because of their small size, less inter and intra-subject variability in gastrointestinal transit time, reduced adverse effects and improved tolerability, no risk of dose dumping, flexibility in design and finally improve stability. However, there are some drawbacks in this system, which include lack of manufacturing reproducibility, high cost of production, multiple formulation steps and also the need of advanced technologies.

There are different types of multiparticulate systems and these are enumerated and explained below:

1. Pulsatile System Based on Rupturable Coating

This is a multiparticulate system in which drug is coated on non-pareil sugar seeds followed by a swellable layer and an insoluble top layer [51, 52]. The swelling agents used include superdisintegrants like sodium carboxymethyl cellulose, sodium starch glycylate, L-hydroxypropyl cellulose, etc. Upon ingress of water, the swellable layer expands, resulting in rupture of film with subsequent rapid drug release. The release is independent of environmental factors like pH and drug solubility. The lag time can be varied by varying coating thickness or adding high amounts of lipophilic plasticizer in the outermost layer.

2. Time controlled expulsion system

This system is based on a combination of osmotic and swelling effects. The core contains the drug, a low bulk density solid and/or liquid lipid material (e.g., mineral oil) and a disintegrant. The core is further coated with cellulose acetate. Upon immersion in aqueous medium, water penetrates the core displacing the lipid material. After the depletion of lipid material, internal pressure increases until a critical stress is reached, which results in rupture of the coating material [53]. Another system is based on a capsule or tablet composed of a large number of pellets consisting of two or more pellets or part [54].

3. Pulsatile Delivery by Change in Membrane Permeability

The permeability and water uptake of acrylic polymers with quaternary ammonium groups can be influenced by the presence of different counter-ions in the medium [55]. Several delivery systems based on this ion exchange have been developed. Eudragit RS 30D is reported to be a polymer of choice for this purpose [56]. It typically contains positively polarized quaternary ammonium group in the polymer side chain, which is always accompanied by negative hydrochloride counter-ions. The ammonium group being hydrophilic it facilitates the interaction of polymer with water, thereby changing its permeability and allowing water to permeate the active core in a controlled manner.

4. Sigmoidal Release System

This consists of pellet cores comprising drug and succinic acid coated with ammonio-methacrylate copolymer USP/NF type B. The time lag is controlled by the rate of water influx through the polymer membrane. The water dissolves acid and the drug in the core. The acid solution in turn increases permeability of the hydrated polymer film. The different types of acids that can be used include succinic acid, acetic acid, glutaric acid, tartaric acid, malic acid, or citric acid [57, 58].
5. Low density floating multiparticulate pulsatile systems
Conventional multiparticulate pulsatile release dosage forms mentioned above are having longer residence time in the gastrointestinal tract and due to highly variable nature of gastric emptying process may result in in vivo variability and bioavailability problems. In contrary, low density floating multiparticulate pulsatile dosage forms reside only in stomach and not affected by variability of pH, local environment or gastric emptying rate. These dosage forms are also specifically advantageous for drugs either absorbed from the stomach or requiring local delivery in stomach [59].

II. Stimuli induced pulsatile release system
Several polymeric delivery systems undergo phase transitions and demonstrate marked swelling-deswelling changes in response to environmental changes including solvent composition, ionic strength, temperature, electric fields, and light [60]. Responsive drug release from those systems results from the stimuli-induced changes in the gels or in the micelles, which may deswell, swell, or erode in response to the respective stimuli. The mechanisms of drug release include ejection of the drug from the gel as the fluid phase synerges out, drug diffusion along a concentration gradient, electrophoresis of charged drugs towards an oppositely charged electrode and liberation of the entrapped drug as the gel or micelle complex erodes [61].

Chemical stimuli induced pulsatile systems
i. Glucose-responsive insulin release devices
In case of Diabetes mellitus there is rhythmic increase in the levels of glucose in the body, requiring injection of the insulin at proper time. Several systems have been developed which are able to respond to changes in glucose concentration. One such system includes pH sensitive hydrogel containing glucose oxidase immobilized in the hydrogel. When glucose concentration in the blood increases glucose oxidase converts glucose into gluconic acid which changes the pH of the system. This pH change induces swelling of the polymer which results in insulin release. Insulin by virtue of its action reduces blood glucose level and consequently gluconic acid level also gets decreased and system turns to the deswelling mode thereby decreasing the insulin release. Examples of the pH sensitive polymers include N, N-dimethylaminoethyl methacrylate, chitosan, polyol etc [62, 63].

ii. Inflammation-induced pulsatile release
On receiving any physical or chemical stress, such as injury, fracture etc., inflammation take place at the injured sites. During inflammation, hydroxyl radicals are produced from these inflammation-responsive cells. Degradation via hydroxyl radicals however, is usually dominant and rapid when Hyaluronic Acid gel is injected at inflammatory sites. Thus, it is possible to treat patients with inflammatory diseases like rheumatoid arthritis; using anti-inflammatory drug incorporated HA gels as new implantable drug delivery systems [64].

iii. Drug release from intelligent gels responding to antibody concentration
There are numerous kinds of bioactive compounds which exist in the body. Recently, novel gels were developed which responded to the change in concentration of bioactive compounds to alter their swelling/deswelling characteristics. Special attention was given to antigen-antibody complex formation as the cross-linking units in the gel, since such interaction is very specific. Utilizing the difference in association constants between polymerized antibodies and naturally derived antibodies towards specific antigens, reversible gel swelling/deswelling and drug permeation changes occurs.

iv. pH sensitive drug delivery system
This type of PDDS contains two components. The first is fast release type while the other is pulsed release which releases the drug in response to change in pH. In case of pH dependent system, advantage has been taken of the fact that there exists different pH environment at different parts of the gastrointestinal tract. By selecting the pH dependent polymers drug release at specific location can be obtained. Examples of pH dependent polymers include cellulose acetate phthalate, polyacrylates, and sodium carboxymethylcellulose. These polymers are used as enteric coating materials so as to provide release of drug in the small intestine [65].
III. External stimuli pulsatile release:
This system was divided into three subparts and is discussed below.

1. Electro responsive pulsatile release
Electrically responsive delivery systems are prepared from polyelectrolytes (polymers which contain relatively high concentration of ionisable groups along the backbone chain) and are thus, pH-responsive as well as electro-responsive. Examples of naturally occurring polymers include hyaluronic acid, chondroitin sulphate, agarose, carbomer, xanthan gum and calcium alginate. The synthetic polymers are generally acrylate and methacrylate derivatives such as partially hydrolyzed polyacrylamide, polydimethylaminopropyl acrylamide [66].

2. Micro electro mechanical systems (MEMS)
A micro fabricated device has the ability to store and release multiple chemical substances on demand by a mechanism devoid of moving its parts [66, 67]. The digital capabilities of MEMS may allow greater temporal control over drug release compared to traditional polymer-based systems. Another development in MEMS technology is the microchip. The microchip consists of an array of reservoirs that extend through an electrolyte-impermeable substrate. The prototype microchip is made of silicon and contains a number of drug reservoirs, each reservoir is sealed at one end by a thin gold membrane of material that serves as an anode in an electrochemical reaction and dissolves when an electric potential is applied to it in an electrolyte solution. The reservoirs are filled with any combination of drug or drug mixtures in any form (i.e. solid, liquid or gel). When release is desired, an electric potential is applied between an anode membrane and a cathode, the gold membrane anode dissolves within 10-20 seconds and allows the drug in the reservoir to be released. This electric potential causes oxidation of the anode material to form a soluble complex with the electrolytes which then dissolves allowing release of the drug. Complex release patterns (such as simultaneous constant and pulsatile release) can be achieved from the microchips. Microchip has the ability to control both release time and release rate.

3. Magnetically induced pulsatile release
The use of an oscillating magnetic field to modulate the rates of drug release from polymer matrix was one of the old methodologies. Magnetic carriers receive their magnetic response to a magnetic field from incorporated materials such as Magnetite, Iron, Nickel, Cobalt etc. For biomedical applications, magnetic carriers must be water-based, biocompatible, non-toxic and non-immunogenic. Mechanistic approach based on magnetic attraction is the slowing down of oral drugs in the gastrointestinal system. This is possible by filling an additional magnetic component into capsules or tablets. The speed of travel through the stomach and intestines can then be slowed down at specific positions by an external magnet, thus changing the timing and/or extent of drug absorption into stomach or intestines [68].

IV. Pulsatile release systems for vaccine and hormone products
Vaccines are traditionally administered as an initial shot of an antigen followed by repeated booster shots to produce protective immunity [69]. The frequency of the booster shots, and hence the exact immunisation schedule is antigen dependent. Also, co-administration of vaccine adjuvant is often required to enhance the immune response to achieve protective immunity [70]. PDDS offer the possibility of single-shot vaccines if initial booster release of the antigen can be achieved from one system in which timing of booster release is controlled. Vizcarra et al. found in nutritionally anoestrous cows, GnRH administered in pulses of 2 mg over 5 min every hour for 13 days produced a higher frequency of luteal activity by 13th day than cows given continuous infusions or pulses every 4 Hr.

Recent Techniques of Oral Time Controlled Pulsatile Technology
Currently, pharmaceutical companies have been focused on developing and commercializing PDDS that fulfil unmet medical needs in the treatment of various diseases. Recently developed technologies are SODAS® Technology, IPDAS® Technology, CODAS™ Technology, GEOCLOCK® Technology, PULSYS™ Technology, Eurand’s pulsatile and Chrono Release System, Magnetic Nanocomposite Hydrogel.

Spheroidal Oral Drug Absorption System (SODAS)
This technology is based on the production of controlled release beads and it is characterized by its inherent flexibility, enabling the production of customized dosage forms that respond directly to individual drug candidate needs. SODAS 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. However, 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 [71].

The Intestinal Protective Drug Absorption System (IPDAS)
This Technology is a high density multiparticulate tablet technology, intended for gastrointestinal irritant compounds. 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 multiparticulates 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 novel controlled release formulation indicated for the treatment of acute and chronic pain.

Chronotherapeutic Oral Drug Absorption System (CODAS)
This technology was designed to release its drug component after a prolonged period of time when administered. A good example is Verelan® PM, which was designed to release Verapamil approximately four to five hours after ingestion. This delay is introduced by the level of release-controlling polymer applied to the drug-loaded beads. The release-controlling polymer is a combination of water-soluble and water-insoluble polymers. When fluid 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 is high [72].

GEOCLOCK® 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 fast release active cores by releasing the inner tablet first after which the surrounding outer shell gradually disintegrates. SkyePharma has used this novel technology to develop Lodotra™, a rheumatoid arthritis drug, which delivers the active pharmaceutical ingredient at the most suitable time of day to treat the disease condition [73].

PULSYS™ Technology
This is an oral drug delivery technology that enables once daily pulsatile dosing. 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.

EURANDs pulsatile and chrono release System
This system is capable of providing one or more rapid release pulses at predetermined times lag. They can
help to 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. When 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 mostly at risk [74].

**Magnetic Nanocomposite Hydrogel**
Magnetic nanocomposite was synthesized by incorporation of super paramagnetic Ferric oxide particles in temperature sensitive poly (N-isopropylacrylamide) hydrogels. High frequency alternating magnetic field was applied to produce pulsatile drug release from nanocomposite hydrogel. Nanocomposites hydrogel are one type of On--Off device where drug release can be turn on by application of alternative magnetic field [75].

**Futuristic Prospect Of PDDS**
The development of pulsatile-release products is very challenging since it requires the correct dose to reach the right site at the appropriate time. Multiparticulate PDDS offer more advantages when compared with the single-unit pulsatile systems since it has predictable, reproducible and short gastric empty time with no risk of dose dumping. However, the novel PDDS pays more attention on site and time-specificity. It is believed that in the near future novel PDDS will be explored in the treatment or management of some other chronic and terminal disease conditions.

**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. Generally, sustained and controlled-release products provide a desired therapeutic effect, but fall short of diseases following biological rhythms. Circadian disorders such as hypertension, osteoarthritis, asthma etc., which require chronopharmacotherapy. PDDS can effectively tackle this problem as it is modulated according to body's circadian clock giving release of drug after a specified time lag. However, for 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 some are currently in the market.

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