A REVIEW ON CHRONOMODULATED DRUG DELIVERY SYSTEMS

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ABSTRACT
Chromomodulated drug delivery systems are gaining a lot of interest as they deliver the drug based on the circadian rhythm of disease. It releases drug at the right place at the right time and in the right amount, increasing patient compliance by reducing dosing frequency. Such systems are designed in such a way that complete and rapid drug release is followed by predetermined lag time; they are also known as pulsatile drug delivery systems (PDDS), time-controlled systems, or sigmoidal release systems. Numerous systems like capsular systems, osmotic systems, single and multiple-unit systems based on the use of pH-sensitive polymers, erodible polymer and swelling hydrophilic polymers have been discussed in the article. These systems are beneficial for the drugs having chronopharmacological behavior such as drug used in treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis like inflammatory disorders. This review article discusses various diseases targeted by pulsatile drug delivery system, types and classification of chronomodulated delivery systems and patented technologies.

INTRODUCTION
Over the past few decades drug delivery systems have drawn an increasing interest due to advancement of the technologies in the pharmaceutical field. The emphasis of pharmaceutical research is turned towards the development of more efficacious drug delivery systems with already existing molecule rather going for new drug discovery because of the inherent hurdles posed in drug discovery and development process.1

Controlled drug delivery systems have gained importance in current pharmaceutical research and development and business. Such delivery systems offers advantage of releasing drug at control rate for prolong period of time and better management in dosage regimen. These dosage forms maintains nearly constant drug level at the site of action, prevents peak plasma fluctuations, reduction in dose of drug, reduced dosage frequency, avoid side effects, and improves patient compliance.1

These new and/or improved delivery systems work on various principles by providing variable/constant drug amounts over a particular time period in our body based on the fact that physiologic parameters display constancy over a time.2 Traditionally drug delivery system was meant only for absorption of drug moiety from gut or site of injection. With new advances in technologies the goal of delivery system improved to provide release of drug at constant rate over prolong/extended period of time with nearly zero order rate.

But living organism do not show such zero order response to every drug. They have predictable resonating dynamic systems, which require different amounts of drug at predictably different times within the circadian cycle which will maximize desired and minimize undesired drug effects.3 Recent studies have revealed that diseases have a predictable cyclic rhythm and that the timing of medication regimen can improve the outcome of a desired effect.4

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).

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transcription of PER While activation of this complex is circadian rhythms. CLOCK / BMAL1 complex, promotes the proteins produced by them are responsible for generating the proteins produced by them are responsible for generating coordinates peripheral oscillators, for functions including cell metabolism. PER (Period genes) and TIM 1-4 genes are part of a feedback loop that regulates the expression of other clock genes.

Human Circadian Rhythm

The term “circadian rhythm” also known as “biological clock” was first described by Halberg and Stephens in 1959. It is present in the suprachiasmatic nucleus (SCN), a pair of distinct groups of cells located in the hypothalamus. SCN creates biological rhythms under the control of clock genes such as PER1, PER2, PER3, CRY1, CRY2, and tau. It also coordinates peripheral oscillators, for functions including cell proliferation and cellular metabolism. PER (Period genes) and the proteins produced by them are responsible for generating circadian rhythms. CLOCK / BMAL1 complex, promotes transcription of PER While activation of this complex is inhibited by the PER1 / PER2 / PER3 / CRY1 / CRY2 / TIM complex. This massive complex acts as a negative auto-feedback system, which has a crucial role in the generation of circadian oscillation. The SCN takes the information on the lengths of the day and night from the retina, interprets it, and passes it on to the pineal gland, a tiny structure shaped like a pine cone and located on the epithalamus. In response, the pineal secretes the hormone melatonin. Secretion of melatonin peaks at night and ebb during the day and its presence provides information about night-length. The SCN receives information on the lengths of the day and night from retina. The retina of the eye contains specialized ganglion cells that are photosensitive and contains a photopigment called as melanopsin. Signals of these cells follow a pathway called the retinohypothalamic tract, which leads to the SCN.
Diseases Targeted by Pdds

Bronchial asthma

Asthma may be the most common disease with the largest circadian variation. Because asthma has such a striking circadian variation, several types of chronotherapy have been tried. The role of circadian rhythms in the pathogenesis and treatment of asthma indicates that airway resistance increases progressively at night in asthmatic patients.

In one study, use of a timed-release formulation of theophylline (Theo 24) achieved therapeutic drug concentrations during the night and avoided toxic levels during the day when the dose was ingested at 3 pm. Another study showed that a single daily dose of inhaled corticosteroids, when administered at 5:30 pm rather than 8 am, was nearly as effective as four doses a day. In addition, oral prednisone has been shown to be much more effective in improving several features of nocturnal asthma.

Cardiovascular disease

Blood pressures (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 aggregation is increased and fibrinolytic activity is decreased in the morning, leading to a state of relative hypercoagulability of the blood.

Heart rate and blood pressure are increased in the early morning hours. The blood pressure declines form mid afternoon and is minimum at midnight, marked rise in blood pressure is observed upon awakening which is called the morning or "a.m." surge. Onset of myocardial infarction has been shown to be more frequent in the morning with 34% events occurring between 6 A.M. and noon. Acute cardiac arrest and transient myocardial ischemia shows an increased frequency in morning. The causes reported for these findings are release of catecholamines, cortisol, increase in the platelet aggregation and vascular tone.

A major objective of chronotherapy for cardiovascular disease is to deliver the drug in higher concentration during time of greatest need and in lesser concentrations when the need is less. ACE inhibitors such as atenolol, nifedipine and amolodipine are more effective when administered during night than morning.

The first chronotherapeutic therapy for hypertension and angina pectoris has recently been developed which matches drug delivery to the circadian pattern of blood pressure and rhythm of myocardial ischemia. Verapamil has been employed in this system where release is observed after a lag time of 4-5 hours and release of verapamil is continued for 18 hours. Taken at bedtime, this provides optimal blood concentration between 4 A.M. and 12 noon.

Data from recent studies demonstrate that antihypertensives and antianginal therapy can be designed to mimic the circadian rhythms. Future research will evaluate whether timings of drug delivery has an effect on the outcomes like control of hypertension, silent ischemia, myocardial infarction and quality of life.

Cerebrovascular accidents

The cerebrovascular accidents have been shown to occur on the first hours of morning between 10 A.M. and 12 noon, and the incidence declines steadily during the evening and the midnight.

Arthritis

The chronobiology, chronopharmacology and chronotherapeutics of pain have been reviewed extensively for instance; there is a circadian rhythm in the plasma concentration of C reactive protein and interleukin-6 of patients with rheumatoid arthritis.

Patients with osteoarthritis tend to have more pain at night and less in the morning in contrast to that patients suffering from rheumatoid arthritis have pain that usually peaks in the morning and decreases as the day progress. 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. From the studies it is revealed that the new cyclooxygenase-2 inhibitors effectively relieve osteoarthritis symptoms when taken in the morning; better results are obtained in rheumatoid arthritis when part of the dose is taken in the evening.

Peptic ulcer disease

Many of the functions of the gastrointestinal tract are subject to circadian rhythms: gastric acid secretion is highest at night (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.

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.

In the past, histamine 2 antagonists were administered at regular intervals around the clock, on the basis of pharmacokinetic properties. However, because maximal acid secretion, peptic ulcer disease pain, and perforation of gastric and duodenal ulcers are more common at night, administration of these drugs at bedtime is more effective. Nocturnal administration not only reduces acid secretion more effectively but also promotes ulcer healing and reduces ulcer recurrence.

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 A circadian rhythm occurs during hepatic cholesterol synthesis.

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. Studies with HMG CoA reductase inhibitors have suggested that evening dosing was more effective than morning dosing.

When the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors were first introduced, morning dosing was recommended. This strategy was re-evaluated after...
the discovery of the circadian rhythm of cholesterol biosynthesis in which higher rates of cholesterol intake and hepatic cholesterologenesis occur during the evening hours, even in the fasting state. One clinical study showed that evening administration of an HMG-CoA reductase inhibitor was more effective at lowering serum cholesterol levels than the same dose given in the morning. Initially, studies involving morning dosing of HMGCoA reductase inhibitors failed to show a reduction in cardiovascular morbidity and mortality. However, the first primary prevention trial that studied evening dosing revealed a significant reduction in serum cholesterol levels as well as rates of such cardiovascular end-points as myocardial infarction, unstable angina, and stroke. On the basis of these findings, it now is recommended that five of the six currently approved HMG-CoA reductase inhibitors are administered between the evening meal and bedtime; atorvastatin calcium (Lipitor) may be an exception because of its long elimination half-life.

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. The blood flow to tumors was threefold greater during each daily activity phase of the circadian cycle than during the daily rest phase. 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.

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. 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.

The colon is also seen as the preferred 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.

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 Pulsatile Drug Delivery System (PDDS).

Pulsatile drug delivery systems, which release the drug rapidly and completely after a lag time, thus provide spatial and temporal delivery and increasing patient compliance, have generated increasing interest during recent years for a number of diseases and therapies. Different types of pulsatile systems have been developed, including eroding and erodible systems.

Advantages of pulsatile drug delivery systems

- Delivery system is designed to release drug based on circadian rhythm of body function or diseases.
- Drug can be targeted to specific sites in gastrointestinal tract i.e colon
- Possible to protect the mucosal layer from harmful effects of irritating drugs.
- Bioavailability of drugs can be improved by reducing the loss due to first pass metabolism.
- Drug release can be modified for extended or prolonged period of time.
- Dosage frequency and dose size can be reduced.
- Reduction in side effects of drug and improved patient compliance can be achieved.
- Less inter subject and intra subject variability.
- Low risk of dose dumping.

Drawbacks of pulsatile drug delivery systems

- Number of process variables is more.
- Low drug loading
- Lack manufacturing reproducibility and efficacy.
- Multiple formulation steps are involved.
- Cost of production is very high.
- Advanced technology is required.
- Trained/skilled person is required.

Classification of Pulsatile Drug Delivery System

Methodologies for PDDS

Methodologies for the PDDS can be broadly classified into four classes; Time controlled pulsatile release

Single unit system

Various types of single-unit capsular pulsatile drug delivery systems have been developed. These include osmosis based systems, PORT systems, rupturable coating systems, swellable or erodible coating systems. Such systems are independent of pH, enzymatic action and intestinal motility. They may be in the form of tablet or capsule or multiple units.
(pellet system). The lag time required before drug release is controlled by the delivery system.

**Osmotic based systems:** This system uses osmotic pressure as energy source to release the drug. It consists of tablet or capsule containing large number of pellets, the core of pellets is composed of drug and osmotic agent. Coating of semipermeable polymeric film is either given to tablet or capsule or pellets. The mechanism of drug release is given in figure 4, when the system imbibes water/GI fluids, osmotic agent present in the core dissolves and exerts osmotic pressure which results in swelling of pellets leading to drug release. Pellets can be designed to give one pulse or many pulses by changing or modifying the coatings.

![Figure 4 Osmotic based tablet system](image)

**PORT® system:** The Port System (Port Systems, LLC) consists of a gelatin capsule coated with a semi permeable polymeric membrane (e.g: cellulose acetate) containing an insoluble plug and an osmotic agent along with the drug formulation. When it comes in contact with the aqueous medium, water diffuses across the semi permeable membrane, resulting in increased osmotic pressure that ejects the plug after a predetermined 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. Figure 5 depicts the mechanism of drug release from the capsular system where the cap dissolves quickly releasing the first immediately dose, after a predetermined lag time insoluble plug is ejected by the osmotic pressure generated from second core containing drug and osmotic agents to give pulse or sustained release second dose.

![Figure 5 Osmotic based capsular system (PORT systems)](image)

**Pulsincap® system:** The Pulsincap® system (Scherer DDS, Ltd) consists of water insoluble capsule body filled with drug formulation and plug, which is expelled out after a predetermined lag time. The capsule body contains swellable plug made up of hydrophilic swelling polymers. When the system gets exposed to water/GI fluids water soluble plug imbibes water swells and expels itself out of the system after a predetermined lag time. This lead to release of drug as a pulse after a lag time. The lag time is dependent on position, dimensions and concentration of polymers used in the plug.

![Figure 6 Pulsincap system](image)

**Multi-particulate system**

Multiparticulate systems (e.g., pellets, beads) offer various advantages over single-unit systems. These systems have no risk of dose dumping, they provide flexibility of blending units with different release patterns, and provide reproducible and short gastric residence time. But the drug-carrying capacity of multiparticulate systems is lower due to presence of higher quantity of excipients. Such systems are a reservoir type with either rupturable or altered permeability coating and generally housed in capsular body.

![Figure 7 Schematic diagram for mechanism of drug release from multiparticulate system](image)

**System Based on Rupturable Coating**

**Rupturable coating systems**

**Time-Controlled Explosion System**

This type of system is multiparticulate system in which drug is loaded through coating on non-pareil sugar seeds followed by a swellable layer and an insoluble top layer. Superdisintegrants like sodium carboxymethylcellulose, sodium starch glycolate, L-hydroxypropyl cellulose are used as swelling agents. Coating polymers used are like polyvinyl acetate, polyacrylic acid, polyethylene glycol, etc. are used. Alternatively, an effervescent system comprising a mixture of tartaric acid and sodium bicarbonate may also be used. Upon coming in contact with water, the swellable layer expands,
resulting in rupture of film coat with subsequent rapid drug release\textsuperscript{66,67}.

**Compression coated tablets**

It consists of core tablet containing drug along with excipients such as disintegrating agents and diluents, which is press coated with polymers. Depending on the thickness of outer coat, water penetrates inside and reaches core tablet. Disintegrating agents present in core tablet swells and ruptures the outer coat releasing drug in form of pulse. Press coated tablet can be designed for timed release by modulating the coat using different types of polymers like swellable, erodible or disintegrable which either erode or collapse form core tablet after a predetermined lag time. The examples of two types can be seen in Figure 8 and 9.

\begin{figure}[h!]
\centering
\includegraphics[width=\textwidth]{Fig8}
\caption{Press coated disintegrating system}
\end{figure}

\begin{figure}[h!]
\centering
\includegraphics[width=\textwidth]{Fig9}
\caption{Press coated disintegrating system}
\end{figure}

**Osmotic-Based Rupturable Coating Systems**

**Permeability Controlled System**

This system is based on a combination of osmotic and swelling effects. This system contains a core containing the drug, a low bulk density solid and/or liquid lipid material (e.g., mineral oil) and a disintegrants. This core is then coated with cellulose acetate. Upon immersion in aqueous medium, water penetrates the core displacing lipid material. After the depletion of lipid material, internal pressure increases until a critical stress is reached, which results in rupture of coating\textsuperscript{68}.

**Delivery by Change in Membrane Permeability**

The permeability and water uptake of acrylic polymers with quaternary ammonium groups (e.g. Eudragit RS 30D) can be influenced by the presence of different counter-ions in the medium\textsuperscript{37}. The ammonium group being hydrophilic facilitates the interaction of polymer with water, and hence changes its permeability and allows water to permeate the active core in a controlled manner. This property is essential to achieve a precisely defined lag time.

**Stimuli induced**

**Site Specific System or 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\textsuperscript{69,70}. 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.

**Chemical stimuli induced pulsatile systems**

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. The 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. Examples of the pH sensitive polymers include \textit{N}, \textit{N}-dimethylaminoethyl methacrylate, chitosan and polyolethane\textsuperscript{71,72}.

\begin{figure}[h!]
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\includegraphics[width=\textwidth]{Fig10}
\caption{Chemical stimuli induces pulsatile system}
\end{figure}

**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\textsuperscript{73}.

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\textsuperscript{74}.
**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. 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.

**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. The digital capabilities of MEMS may allow greater temporal control over drug release compared to traditional polymer-based systems. 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.

**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.

**Osmotic controlled drug delivery (OROS-CT)**

OROS-CT was introduced by Alza Corporation, to target the drug locally to the colon. The system include either single osmotic unit or up to 6 push pull units, each 4 mm in diameter, encapsulated within a hard gelatin capsule. Each push pull unit consists of semi permeable layer and enteric coating with laser drilled orifice. When such system is administered hard gelatin capsule dissolves liberating push pull units. These units cannot absorb fluids/water from stomach because of enteric coating. After reaching colon enteric coating dissolves at the higher pH like greater than 7, the osmotic push compartment swell due to the absorption of the water into the unit, and pushes drug compartment to release drug at controlled rate. This push-pull system was designed for treating ulcerative colitis with a 3-4 h post gastric delay, to prevent drug delivery in the small intestine. OROS-CT units can deliver the drug into the colon for a short period of four hours and to maintain a constant release rate for up to 24 hours. That was the new idea to deliver the drug in colon, and many stability studies, in-vitro/in-vivo evaluation can performed in CDDS.

**Figure 11** Schematics of the conceptual design of CODES™

**Figure 12** Mechanism of drug release from OROS-CT

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, carborner, xanthan gum and calcium alginate. The synthetic polymers are generally acrylate and meth acrylate derivatives such as partially hydrolyzed polyacrylamide, polydimethylaminopropyl acrylamide.

**Figure 13** Schematic diagram for magnetically induced pulsatile release

Pulsatile release systems for vaccine and hormone products

Generally vaccines are administered as an initial shot of an antigen followed by repeated booster shots to produce protective immunity. 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. 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 anorexic cows, GnRH administered in pulses of 2 mg every 5 min for 2 hours on 3 days produced a higher frequency of luteal activity by 13th day than cows given continuous infusions or pulses every 4h.

**Recent Advances in Pulsatile Drug Delivery Systems** 54,55,56,57

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<thead>
<tr>
<th>S.No</th>
<th>Technology</th>
<th>Mechanism</th>
<th>Innovator’s name/ Marked names/ Present name</th>
<th>Company</th>
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<td>OROS®</td>
<td>Osmotic Release Oral System. The system uses osmotic pressure as energy source for releasing drug</td>
<td>Concerto®/Mellithimetate, Procarda XL®, Nifedipine, Jaup®; Paliperidone, Dizor®</td>
<td>Alza Corporation</td>
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<td>2</td>
<td>ACCU-Break</td>
<td>Unique tablets that contain drug free layer which can be split into exact half for easy and precise dose adjustment.</td>
<td>ACCU-DTM® bilayer tablet, ACCU-TM® bilayer tablet</td>
<td>Accu-Break Pharmaceuticals Inc., Plantation FL</td>
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<td>SODAS® Technology</td>
<td>Spherical Oral Drug Absorption System. Available in the form of once-daily profile and extended-release formulations with a bi-modal release profile</td>
<td>Afladial®, a once-daily indelipine</td>
<td>Elan’s Drug Technologies</td>
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<td>4</td>
<td>MXDASS® Technology</td>
<td>Matrix Drug Absorption System. It contains drug in a blend of hydrophilic polymer matrix, which controls release rate of drug through a process of diffusion and erosion in the gastrointestinal tract. The Intestinal Protective Drug Absorption System.</td>
<td>Verapanil is formulated as VERELAN</td>
<td>Elan’s Drug Technologies</td>
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<td>5</td>
<td>IPDASS® Controlled-Release Technology</td>
<td>Composed of high-density multiparticulate controlled-release technology, designed for use with more gastrointestinal irritant compounds. Chronoabsorb Oral Drug Absorption System.</td>
<td>Naprosyn formulation, Naprelan®</td>
<td>Elan’s Drug Technologies</td>
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<td>6</td>
<td>CODASS® Technology</td>
<td>It consists of miniblades filled in hard gelatin capsules</td>
<td>Dual Release Drug Absorption System bilayer tablet, Combines an immediate-release granulate and a modified-release hydrophilic matrix complex as separate layers within the tablet.</td>
<td>Elan’s Drug Technologies</td>
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<td>7</td>
<td>PRODAS® Technology</td>
<td>Programmable Oral Drug Absorption System. It consists of miniblades filled in hard gelatin capsules</td>
<td>Dual Release Drug Absorption System bilayer tablet, Combines an immediate-release granulate and a modified-release hydrophilic matrix complex as separate layers within the tablet. Which can provide immediate or sustained release of two drugs or different release rates of the same drug in one dosage form.</td>
<td>Elan’s Drug Technologies</td>
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<td>8</td>
<td>DUREAS™ Technology</td>
<td>Drug release can be modified for achieving immediate and sustained release for different drugs or same drug.</td>
<td>Drug release can be modified for achieving immediate and sustained release for different drugs or same drug.</td>
<td>Elan’s Drug Technologies</td>
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<td>9</td>
<td>Geoclock™</td>
<td>This technology is used for once daily pulsatile dosing. Compresse used that contains pellets designed to release drug at different regions in the GI tract in a pulsatile manner. It consists of cylindrical miniblades (2 mm diameter) for controlled release</td>
<td>Geoclock™ is a validated oral drug delivery technology that can be used to release the drug from the tablet after a pre-determined lag-time that is independent of food or pH.</td>
<td>Skypharma PLC, UK</td>
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