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PULSATILE DRUG DELIVERY SYSTEM: A NOVEL APPROACH FOR DRUG DEVELOPMENT

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ABSTRACT

The pulsatile drug delivery system offers various advantageous characteristics by delivery of the drug at the right time based on the circadian rhythm of the body. The basic principle for the use of pulsatile release of the drugs is where a constant drug release is not desired. A pulse has to be designed in such a way that a complete and rapid drug release is achieved after the lag time. This concept benefits many patients for the treatment of various diseases like asthma, arthritis, cancer, diabetes, hypertension, ulcer, hypercholesterolemia, congestive heart failure, stroke. This review paper aims to introduce the basic concept of chronotherapeutics, drug release mechanism, formulation types through different classification systems based on time-controlled, stimuli induced, external stimuli induced. This review also covers the marketed innovations of pulsatile drug conveyance like PulsincapTM, OROS, CODAS, 3D printing, CONTIN**.** Pulsatile drug delivery systems have the potential to bring new developments in the therapy of many diseases.

KEYWORDS: lag time, pulsatile drug delivery system(PDDS), circadian rhythm, drug release, chronotherapeutics.

INTRODUCTION

Androsthenes noticed that the leaves of specific trees open during the day and close in evening time showing clear rhythmicity. In 1729, the French stargazer Jean Jacques d'OrtousdeMairan led the main known examination on biological rhythms.[1] Biological rhythm directs manybody functions in animal's viz., digestion, physiology, conduct, rest designs, chemical creation, and so forth. The degree of cortisol is higher toward the beginning of the day hours, and its delivery is accounted for to decay continuously during the day. Pulse is high toward the beginning of the day and afterwards drops off during the evening.[2] There are sure conditions under which such a release pattern after a lag time is not appropriate for demanding the release of a drug. Thus pulsatile drug delivery system (PDDS) is required in such conditions. The pulsatile mechanism is gaining satisfying attention because the drug is completely released after a given lag time. The pulsatile conveyance of medications is a time and site precise conveyance of medications, consequently giving spatial and timely distribution and expanding patient consistence.[3] Pulsatile drug conveyactive ingredient completely and quickly after a defined lag time.[4]

Chronobiology is the science worried about the biological mechanism of the diseases as per a period structure. "Chrono" relates to time and "science" relates to the examination, or science, of life.[5] There are three types of mechanical rhythms in our body, they are: Circadian, Ultradian, Infradian Rhythm Oscillations that are longer than 24 hours (short of what one cycle for every 24hours) are named as Infradian Rhythms for example month to month Menstruation. Ultradian Rhythms Oscillations of a more limited span are named Ultradian Rhythms (more than one cycle for every 24 h) For example an hour and a half rest cycle. Circadian Rhythms are self-supporting, endogenous motions that happen with a periodicity of around 24 hours. These rhythms permit living beings to expect and plan for exact and standard climate changes. There are clear examples of core body temperature, brain action, hormone production, and other natural exercises connected to this cycle(figure 1) A few groups of people work best toward the beginning of the day while others have their top in the early afternoon or evening. If our normal rhythm is disrupted we will, in general, get restless e.g. various individuals to experience issues in changing by swing shift work plans.[6,7] Chronopharmacology is the science worried about the varieties in the pharmacological activities of different medications throughout some undefined time frame of the day.Chronotherapy is the co-ordination of natural rhythms and clinical treatment.[5]

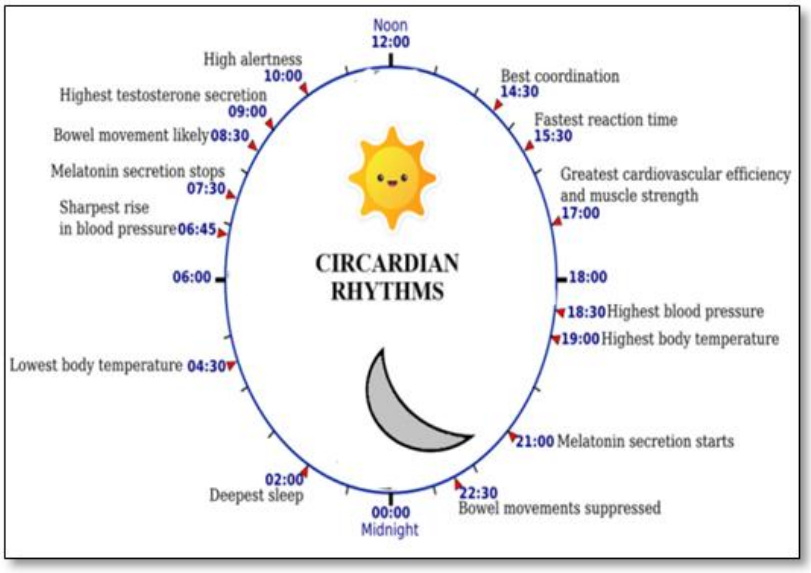

Figure 1: Circadian rhythm cycle.

Need of pulsatile drug delivery system

Many body functions follow circadian rhythm, i.e., their movement increments or diminish with time. Various chemicals like rennin, aldosterone, and cortisol show day by day just as convenient changes in their blood levels. Acid secretion, gastric release, cholesterol production, and gastrointestinal blood transfusion may change with the circadian mood. Many drugs (e.g. peptide drugs) which will degrade in acid medium and irritate the gastric mucosa or induce nausea and vomiting lag time is essential for them. Drugs which undergoes through broad first pass absorption that easily given by pulsatile drug conveyance framework. Drugs that produce biological tolerance due to continuous exposure to medication in the body. This system tolerance by giving lag time.[8]

Table 1: Diseases requiring pulsatile delivery.[8,10]

Chronological behavior	Drug used	Disease
Exacerbation more common during the sleep period & attacks after 12 PM or at early morning hours	β2 agonist, Antihistamines	Asthma
Cholesterol synthesis is generally higher during night than day time	HMG CoA reductase inhibitors	Hypercholesterolemia
Increased blood sugar level after meal	Sulfonylurea, Insulin	Diabetes mellitus
Acid secretion high in daylight and at nighttime	H2 blockers	Peptic ulcer
Blood pressure is lowest during sleep and rises in early morning	Nitroglycerin, calcium channel blocker, ACE inhibitors	Hypertension
Pain in the morning & more pain at night	NSAIDs, Glucocorticoids	Rheumatoid arthritis
Chest pain and ECG changes more common in early morning	Antianginal drugs	Angina Pectoris

Benefits of PDDS

Pulsatile drug delivery system is a novel technique which creates the interest to manufactures to create the medication like drugs focusing on specific sites like colon to decreases side effects and lower the everyday cost to the patient because fewer dosage units are needed by the patient in therapy.[5] Chronotherapypostpone the discharge and gives an ideal treatment of diseases. The framework can be used for different solid dosage forms which incorporate granules, microspheres, microparticles, tablets. It increases absorption and bioavailability than regular prompt delivery or supported delivery drug because of its capacity to deliver the drug in a burst way, at the target site of retention.[9] This system also worked to avoid biological tolerance (for example Transdermal nitroglycerine) and drug mislaying is prevented by broad first-pass metabolism (for example proteins and peptides).[6]

Limitations of PDDS

Pulsatile drug delivery systems have certain limitation, so in many cases these drug delivery system is failing, likedrug loading capacity is limited which leads to inadequate arrival of medication. The Production is overpriced, large number of process variables, lack of manufacturing reproducibility and efficacy. Invitro-in vivo correlations are immeasurable.[6] It requires

trendsetting innovation technology, large number of detailing steps and trained personnel.[10]

Mechanism of drug release from pulsatile drug delivery system [11]

Diffusion: In the gastrointestinal tract: When particles come in contact with aqueous fluid then water diffuses into the interior of the particle and cause the diffusion of drug solution across the release coat to the outside. The process shows the movement of drug molecules from a region of a higher concentration to one with a lower concentration.

Erosion: Some coatings can be intended to dissolve steadily with time, consequently delivering the medication contained inside the molecule. Disintegration might be of two sorts arebulk erosion and surface erosion.

Osmosis: It is the net development of solvent molecules through a selectively permeable membrane into a region of higher solute concentration, in the direction that tends to equalize the solute concentrations on the two sides. This framework encapsulating an osmotic drug core containing an osmotically active medication inside a semi penetrable film produced using biocompatible polymer like cellulose acetic acid.

Classification of pulsatile drug delivery system[9,12,13,14]

Pulsatile drug delivery system classified into three major classes;

Time controlled pulsatile drug delivery

Stimuli induced pulsatile drug delivery

Externally regulated pulsatile drug delivery

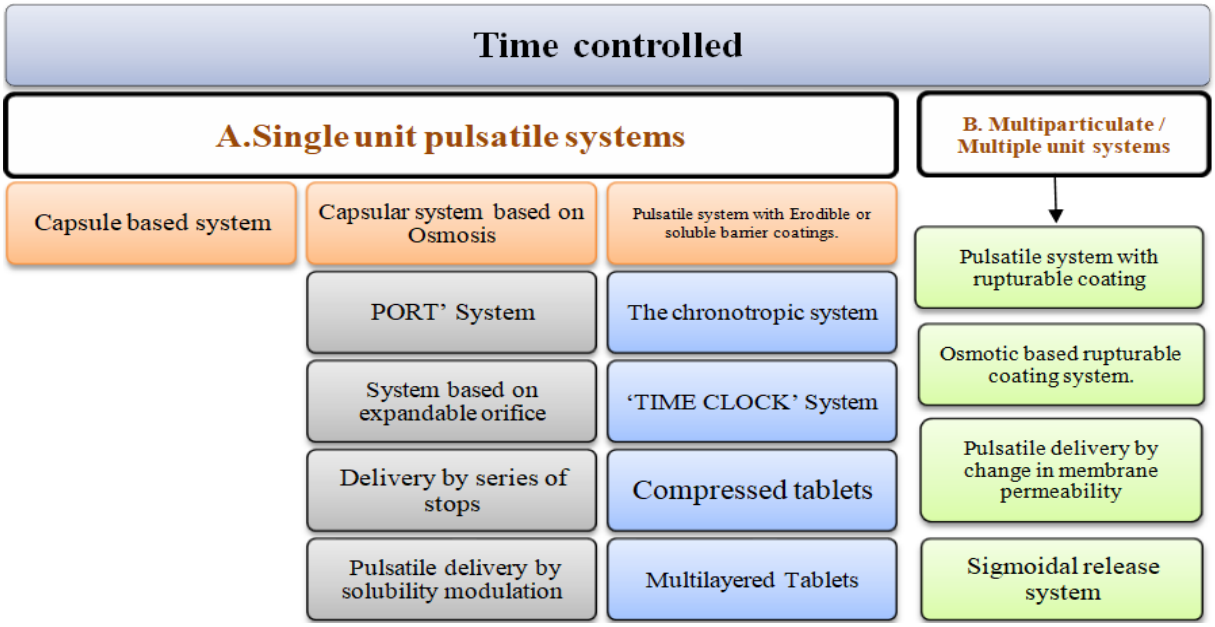

Figure 2: Time controlled pulsatile drug delivery.

Single unit pulsatile systems are developed by the use of erodible or breakable coating on core material; it is either in capsule form or in osmotic based type formulation.[15]

Capsule based system: Single unit dosage forms are altered in capsule form conveyance of the medication. In this framework, lag time is controlled by a plug, which gets pushed away by swelling or erosion and the medication is discharged as a pulse from the insoluble casing. By manipulating the dimension and the position of the plug, the lag time can be controlled. This type of case contains hydrogel and gelatin. Several polymers are used for this technique such as polyvinyl alcohol, pectin, glycerol monooleate, Polyethylene oxide.[7,10]

Capsular system based on osmosis

The fundamental in this osmotic system is a capsule enclosed with a semi-porous film. The capsule contains an osmotically active agent, an insoluble plug and a therapeutically active agent. When this case comes in contact with the body liquid, the semi-permeable film allows the entry of liquid, which causes the pressure to develop and the insoluble plug is removed because of the pressing factor after a lag time.[12,16]

PORT' System

The Port framework was created by the Therapeutic framework research lab Ann Arbor, Michigan, USA. It comprises a case covered with a semi-porous film. Inside the case was an insoluble plug comprising of the osmotically active ingredient and the medication. At the point when this case interacted with the body liquid, the semipermeable layer permitted the entry of water, which made the pressing factor create and the insoluble plug expelled after a lag time.[17, 18]

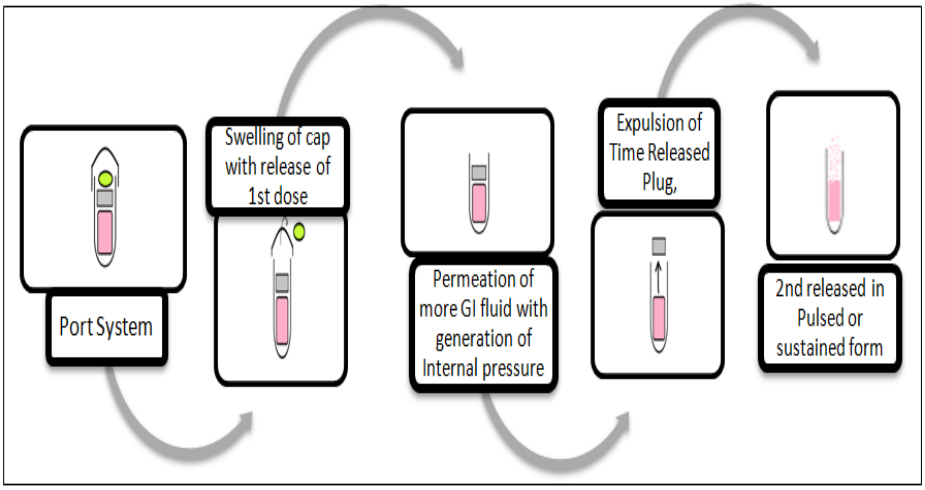

Figure 3: Drug release mechanism from port system.

System based on expandable orifice

To convey the medication in fluid form, an osmotically drive capsular framework created in which the liquid drug is absorbed into profoundly permeable particles, which delivers the drug through an orifice of a semi-permeable case built up by an extending osmotic layer after the hindrance layer is broken down. This framework has the advantages of extended release with high bioavailability.[17,9] For conveying insoluble medications (Polypeptides and Polysaccharides), liquid environment favours solubilization, dispersion and protection from enzymatic degradation.[16] The capsular framework conveys medication by the capsules osmotic blend of moisture from the body. The capsule wall, made up of an elastic material, also have an orifice. The capsule wall stretches due to increase in the pressure due to osmosis. When elastic wall relaxes, the flow of drug through orifice stops because the orifice is small enough. But when the elastic wall is swells beyond threshold value, the orifice magnify to allow at required rate to release the drug. Styrene-butadiene copolymer such as elastomer is generally used.[5]

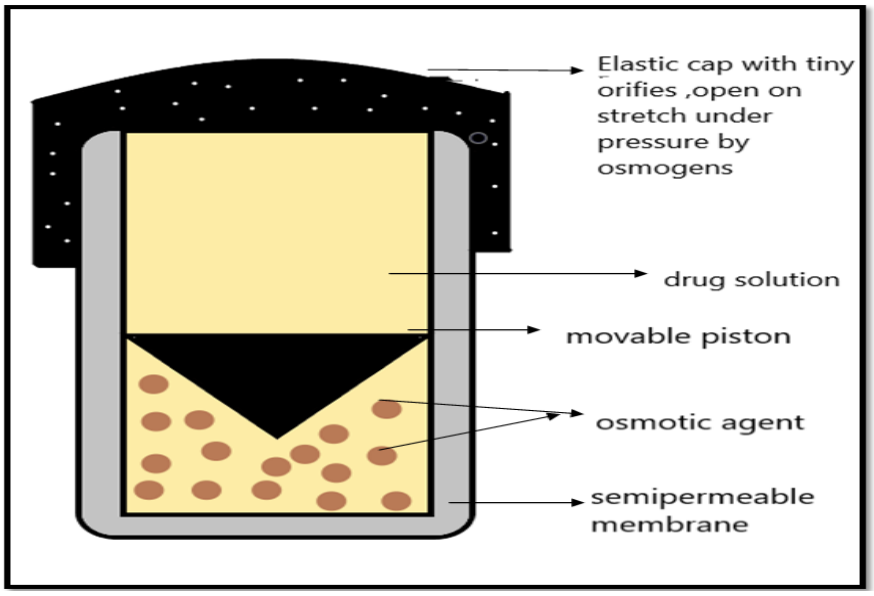

Figure 4: System based on expendable orifices.

Delivery by series of stops

It is for an implantable capsule. It contains medication and water osmotic motor put in compartments isolated by a movable partition. Pulsatile drug conveyance is accomplished by series of stops. Series of stops block the development of medication and gives a lag time which is defeated as the osmotic pressure rises above a threshold level. The number of stops and the longitudinal arrangements of the stops along the length of the capsule direct the number and frequency of the pulses, and the design of the partition controls the pulse force. This framework was utilized to convey porcine somatotropin.[5,8,17]

Pulsatile delivery by solubility modulation

Magruder created framework comprises of different solubility modulators. This system was particularly created for the conveyance of salbutamol sulfate. The

creations contain the medication (salbutamol sulfate) and a modulating agent (sodium chloride). The amount of sodium chloride was not exactly the sum expected to keep up immersion in a liquid that enters the osmotic device. It gives pulse discharge.[8,17]

Pulsatile system with Erodible or soluble barrier coating

In these systems the drug release is controlled by the dissolution or erosion of the outer coat which is applied on the core containing a drug. The time dependent release of the active ingredient can be obtained by optimizing the thickness of the outer coat. An oral dosage form devised which use to release drugs subsequent in a deliberate time period after administration based on this concept. This system is composed of a drug-containing core and a hydrophilic swellable polymeric coating of HPMC, which is capable of delaying the drug release through slow interaction with aqueous fluids.[12,1]

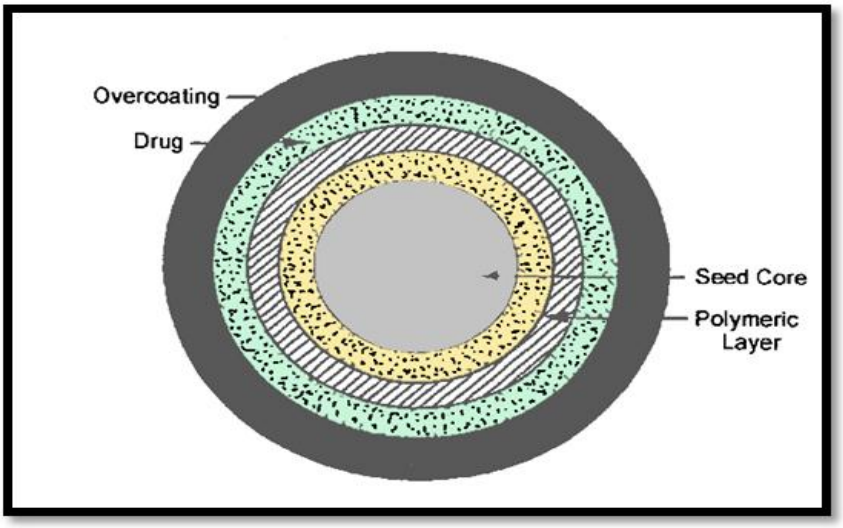

Figure 5: Pulsatile system with erodible or soluble barrier coating.

The chronotropic system

It consists of a drug-containing core coated by hydrophilic swellablehydroxyl propylmethyl cellulose (HPMC), which is responsible for a lag phase in the onset of release. In addition, through the application of an outer gastric-resistant enteric film, the variability in gastric emptying time can be overcome, and a colon-specific release can be obtained, relying on the relative reproducibility of small intestinal transit time. The lag time is controlled by the thickness and the viscosity grades of HPMC.[19]

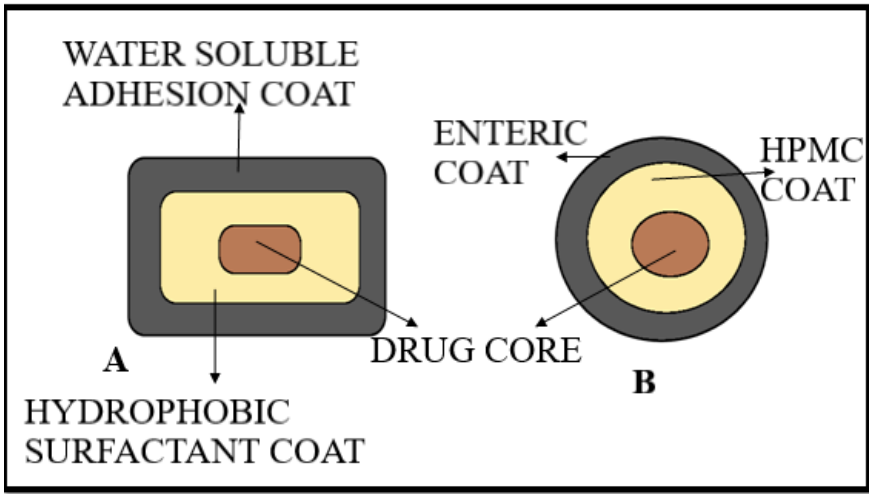

Figure 6: A) Time clock system B) Choronotropicsystem.

Time clock‟ System

In his system, the core releases the drug immediately after the rehydration of the dosage form. Low calorie and high-calorie meal may influence the system.[10]

Compressed tablets

Compression covering includes direct pressure of both the core and the coat. The external tablet of the compression coat tablet gives the first dose, quickly disintegrating in the stomach and the inward layer is

formed with segments that are insoluble in gastric media however are delivered in the intestinal climate. Cellulose derivatives might be utilized for this reason.[9,10]

Multilayered tablets

A delivery design with two pulses was acquired from a three-layered tablet containing two medication containing layers isolated by a medication-free gellable polymeric barrier layer. This three-layered tablet coated on three sides within impermeable ethylcellulose, and the top segment left uncoated. Upon contact with the dissolution medium, the initial dose portion joined into the top layer release quickly from the non-covered surface. The second pulse was obtained from the bottom layer after the gelling barrier layer of HPMC was eroded and dissolved. The rate of gelling and/or dissolution of the barrier layer control the appearanceof the second pulse.[20] The gelling polymers incorporate cellulose derivatives like HPMC, methylcellulose, or polyvinyl alcohols of different molecular weights and the coating materials include ethylcellulose, cellulose-acetate propionate, acrylic and methacrylic copolymers and polyalcohols.[9]

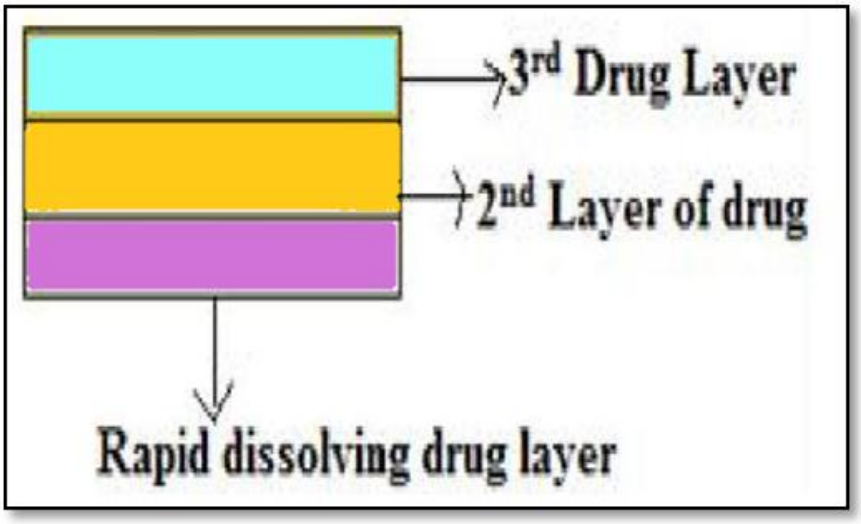

Figure 7: Multilayered tablets.

Multiparticulate / Multiple unit systems

The designing multiparticulate dosage form has more advantages than a single unit dosage form. The mechanism by which the drug is released from pellets depends on the type of coating, insoluble coating under all physiological conditions, pH-dependent coating whose solubility changes dramatically at some point in GI tract and slowly erodes coating. The method of preparation and processing parameters are affected on pellets preparation.[8]

Pulsatile system with rupturable coating

These systems depend on the disintegration of the coating for the release of a drug. The pressure necessary for the rupture of the coating can be achieved by effervescent excipients, swelling agents, or osmotic pressure. An effervescent mixture of citric acid and sodium bicarbonate was incorporated in a tablet core coated with ethyl cellulose. The carbon dioxide developed after penetration of water into the core resulted in a pulsatile release of drug after rupture of the coating. The release may depend on the mechanical properties of the coating layer**.** E.g. Time –controlled explosion system (TCES).[7,17] It is reported that the weak and non-flexible ethylcellulose film ruptured sufficiently as compared to more flexible films. The lag time increases with increasing coating thickness and increasing hardness of the core tablet. Highly swellable agents/ superdisintegrants (cross carmellose, sodium starch glycollate, and low substituted hydroxypropylcellulose) were also used to design a capsule-based system comprising a drug, swelling agent, and rupturable polymer layer. The swelling of these materials resulted in a complete film rupture followed by rapid drug release. The lag time is the function of the composition of the outer polymer layer. The presence of hydrophilic polymer like HPMC reduces lag time. The system can be used for the delivery of both solid and liquid drug formulations.[9]

Osmotic based rupturable coating system

This system is based on a combination of osmotic and swelling effects. The core contains a drug, a low bulk density solid and/or liquid lipid material (For example mineral oil) and a disintegrant. The core is finally coated with cellulose acetate. On immersion in an aqueous medium, water penetrates the core displacing lipid material. After the depletion of lipid material, internal pressure increases until critical stress is reached, which results in rupture of the coat.[13,21]

Pulsatile delivery by a 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.

Eudragit is a polymer of choice for this purpose. It typically contains a positively polarized quaternary ammonium group in the polymer side chain, which is always accompanied by negative hydrochloride counter-ions. The ammonium group being hydrophilic facilitates the interaction of the polymer with water, thereby changing its permeability and allowing water to permeate the active core in a controlled manner. This property is essential to achieve a precisely defined lag time. The cores prepared using theophylline as model drug and sodium acetate. These pellets coated using Eudragit (10% to 40% weight gain) in four different layer thicknesses. A correlation between film thickness and lag time was observed. It was found that even a small amount of sodium acetate in the pellet core had a dramatic effect on the drug permeability of the Eudragit film. After the lagtime, the interaction between the acetate and polymer increases the permeability of the coating so significantly that the entire active dose is liberated within a few minutes. The lag time increases with the increasing thickness of the coat, but the release of the drug was found to be independent of this thickness and depended on the amount of salt present in the system.[7,21]

Sigmoidal release system

This consists of a pellet containing drug and succinic acid coated with ammonia methacrylate copolymer. The water in the medium dissolves succinic acid. The drug inside and the acid solution increase the permeability of the polymer film. Instead of succinic acid, acetic acid, glutaric acid, tartaric acid, malic acid, or citric acid is also used.[13]

Stimuli induced pulsatile drug delivery

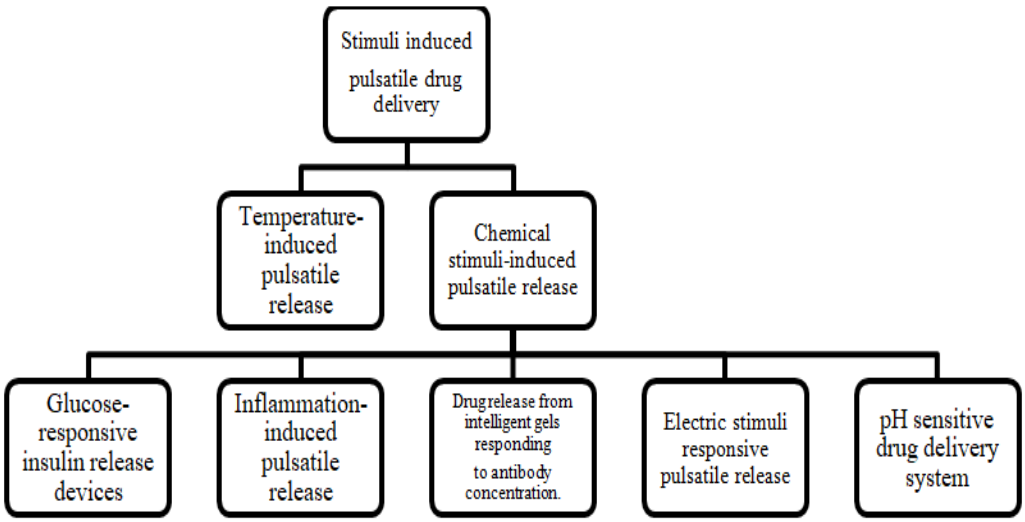

Figure 8: Stimuli induced pulsatile drug delivery.[7, 9]

Temperature-induced pulsatile release

A few polymeric conveyance frameworks go through the stage and demonstrate marked swelling-deswelling phase because of temperature which regulates arrival of medication in the swollen state, for example, thermo-responsive hydrogel systems. Bae et al., (1995) created an indomethacin pulsatile discharge design in the temperature ranges between 200^0C and 300^oC by utilizing reversible swelling properties of copolymers of N-isopropyl acryl amide and butyrylacrylamide.

Kataoka et al., (2001) developed the thermosensitive polymeric micelles as medication transporter to treat cancer. They utilized end-functionalized poly (N-isopropyl acryl amide) (PIPAAm) to plan the crown of the micelle which showed both hydration and dehydration behavior with change in temperature.[22,23,24]

Chemical stimuli induced pulsatile systems

Glucose-responsive insulin release devices

In the event of Diabetes mellitus, there is a rhythmic increase in the degrees of glucose in the body, requiring the injection of insulin at the appropriate time. A few frameworks have been created which can react to changes in glucose concentration. One such framework incorporates pH delicate hydrogel containing glucose oxidase immobilized in the hydrogel. At the point when glucose concentration in the blood expands glucose oxidase changes over glucose into gluconic acid which changes the pH of the framework. This pH change incites expansion of the polymer which brings about insulin discharge. Insulin by under its activity diminishes blood glucose level and therefore gluconic acid level additionally gets diminished and framework goes to the deswelling mode thereby diminishing the insulin discharge. Example of the pH-sensitive polymers incorporates N, N-dimethylamino ethyl methacrylate, chitosan, polyol.[25,26]

Inflammation-induced pulsatile release

At the point when individuals get physical or chemical pressure, like injury, broken bones, and so on, inflammation responses occur at the harmed locales. During inflammation, hydroxyl radicals are created from

these inflammation responsive cells. Degradation through hydroxyl radicals, however, is normally prevailing and fast when the hyaluronic acid gel is injected at provocative locales. Subsequently, it is feasible to deal with patients with provocative sicknesses like rheumatoid joint pain; utilizing mitigating drug fused HA gels as new implantable medication conveyance system.[27]

Drug release from intelligent gels responding to antibody concentration

There are various sorts of bioactive mixtures which exist in the body. Recently, novel gels were created which responded to the change in concentration of bioactive mixtures to modify their expanding/ deswelling qualities. Extraordinary consideration was given to antigen-immune response complex development as the cross-connecting units in the gel since such association is particular. Using the difference in constants between polymerized antibodies and naturally derived antibodies towards specific antigens, reversible gel growing/deswelling and drug permeation changes occurs.[16]

Electric stimuli-responsive pulsatile release

Electric improvements initiated drug discharge framework utilizing the electrically stimulated swelling/deswelling qualities of polyelectrolyte hydrogel. The gels exhibited reversible swelling / shrinking behavior in response to on-off switching of an electric stimulus. Thus, drug molecules within the polyelectrolyte gels might be squeezed out from the electric stimuli-induced gel contraction along with the solvent flow. To realize this mechanism, poly (sodium acrylate) microparticulate gels containing pilocarpine as a model drug were prepared.[27]

PH-sensitive drug delivery system framework

Such kind of pulsatile drug conveyance framework contains two segments one is of instant release and another one is pulse discharge which delivers the medication in light of progress in pH. In the event of pH subordinate framework advantage has been taken off the way that there exists distinctive pH climate at various pieces of the gastrointestinal tract. By choosing the pH depended on polymers drug discharge at a specific area can be obtained. An illustration of pH subordinate polymers incorporates cellulose acetate phthalate, polyacrylates, and sodium carboxymethylcellulose. These polymers are utilized as enteric covering materials to givethe arrival of medication in the small intestine.[5]

External stimuli induced system

These types of open-loop frameworks are not self-directed. Be that as it may, for the conveyance of the medication in pulse way another manner by which medication discharge in the modified example can be the external regulated system. These frameworks are magnetically stimulated, ultrasonically regulated and photo stimulated.[8]

Micro electro mechanical systems (MEMS)

A miniature created device can store and delivery numerous compound substances on demand by an mechanism without moving its parts. The improvement in MEMS innovation is the microchip. The microchip made of an array of reservoirs that widen up by an electrolyte impermeable substrate. The prototype microchip is made of silicon and contains various medication supplies, every reservoir is fixed toward one side by a thin gold film of material that fills in as an anode in an electrochemical response and dissolves when an electric potential is applied to it in an electrolyte arrangement. The reservoirs are loaded up with any blend of medication or medication combinations in any structure (for example solid, fluid or gel). At the point when delivery is wanted, an electric potential is applied between an anode layer and a cathode, the gold film anode dissolves inside 10-20 seconds and permits the medication in the reservoirs to be delivered. This electric potential makes oxidation of the anode material structure a solvent complex with the electrolytes which at that point dissolves permitting arrival of the medication. Microchip has the ability to control both delivery time and delivery rate. [26,18]

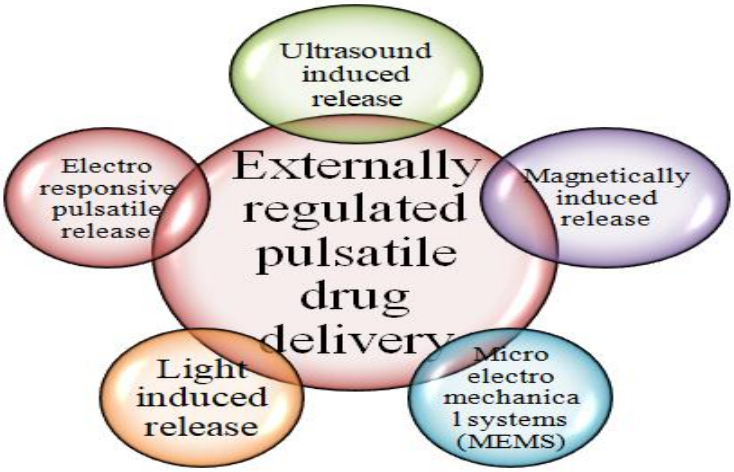

Figure 9: Externally regulated pulsatile drug delivery.

Magnetically induced release

Magnetic transporters get their magnetic reaction to anmagnetic field from fused materials like magnetite, iron, nickel, cobalt and so on magnetic –sensitive performance of ferrogels for controlled arrival of medication was studied by Tingyu Liu, et al. A smart attractive hydrogel (ferrogel) was manufactured by blending poly (vinyl liquor) hydrogel and Fe3O4 magnetic particles through freezing-thawing Cycles. Although the external direct current magnetic field was applied to the ferrogel, the medication got amassed around the ferrogels, however the gathered medication spray to the environment in a split second when the magnetic fields immediately exchanged "off". Moreover, rapid slow drug release could be tunable while the magnetic field was switched from "off" to "on" mode.[25,26,29]

Ultrasonically modulated system

It is for the most part utilized as an enhancer for the improvement of medication permeation through biological boundaries, like skin, lungs, intestinal walls and blood vessels. Mechanism mostly included here is the absorption of acoustic energy by the liquids or tissues and oscillating bubbles cause non warm impact alongside the non cavitational impacts, for example, radiation pressure, radiation force and acoustic streaming Ultrasonic waves cause the disintegration of the polymeric network modulating drug discharge. Miyazaki et al., (1998), assessed the impact of ultrasound (1 MHz) on the delivery rate of bovine insulin from ethylene vinyl liquor copolymer networks and supply type drug conveyance frameworks in which they discovered sharp drop in blood glucose levels after utilization of ultrasonic waves.[22,30,31]

Electro responsive pulsatile release

The system gives the medication discharge by activity of applied electric field on rate limiting membrane and additionally on solute, subsequently controls transport across the layer. The polymer has two redox states, just one of which is reasonable for ion binding. Medication particles are bound in redox state and release. The system of medication transport of proteins and natural solutes across hydrogel layers. Electrically induced swelling of layer to adjust effective pore size and penetrability. Electrophoretic and electro osmotic agumentation of solute flux inside a layer. Electrostatics partitioning of charged solutes in charged membrane.[8]

Photo stimulated system

The association of light and material can be utilized to regulate drug conveyance. This can be refined by joining a material that retains light at an ideal wavelength and a material that utilizations energy from the absorbed light to regulate drug conveyance. Installing the nanoshells in lN-isopropylacrylamide-co-acrylamide (NIPAAm-co-AAM) hydrogel formed the necessary composite material. When presented to near infrared light, nanoshells ingest the light and convert it to heat, raising the temperature of composite hydrogel over its lower critical solution temprature (LCST). That is bringing about the expansion rate arrival of the medication from matrix framework. Light-sensitive hydrogel have possible applications in creating optical switches, display units, and ophthalmic medication delivery devices.[17]

Marketed innovations of pulsatile drug conveyance

Pulsincap™ innovation

Pulsincap was created by R.R. Scherer International Corporation (Michigan). This device consists of a non-disintegrating half capsule body sealed at the open end with a hydrogel plug that is covered by a water-soluble cap. The whole unit is coated with an enteric polymer to avoid the difficulty of variable gastric emptying. When this capsule comes in contact with the dissolution fluid, it swells, and after a lag time, the plug pushes itself outside the capsule and rapidly releases the drug.[32] one more formulation approach was in the form of a bead or granule with a four-layered spherical composition, which consists of a core, a drug, swelling agent (e.g., sodium starch glycolate or carboxymethyl cellulose sodium) and an outer membrane water-insoluble polymer (e.g., ethylcellulose, Eudragit® RL). The penetration of GI fluids through the outer membrane causes the expansion of the swelling agent. The resulting stress due to swelling force leads to the destruction of the membrane and subsequent rapid drug release. Polymers used for designing the hydrogel plug were various viscosity grades of hydroxyl propyl methyl cellulose, polymethylmethacrylate, polyvinyl acetate and polyetheneoxide.[6]

Diffucaps® innovation

It was created by R. P. Scherer International Corporation, Michigan, US. Diffucaps®, consist of one or more populations of drug-containing particles (beads, pellets, granules, etc.). Each bead population exhibits a pre-designed rapid or sustained release profile, with or without a predetermined lag time of 3 – 5 hours.[33] This multiparticulate bead system comprised of multiple layers of drug, excipients and release-controlling polymers. The beads contain a layer of organic acid or alkaline buffer to manage the solubility of a drug by creating an optimal PH microenvironment for drugs that exhibit poor solubility in intestinal pH, in environments with pH greater than 8.0 or in physiological fluids. Diffucaps® beads are < 1.5 mm in diameter and can be filled into capsules or compressed into orally disintegrating tablets. In addition, for patients who experience difficulty in swallowing tablets or capsules, Diffucaps® products are produced in capsules that allow the capsules to be opened and the contents used as a sprinkle on foods, providing a flexible dosage form.[34]

Orbexa® Technology

Orbexa® Technology: Developed by Aptalis Pharmaceutical Technologies. Orbexa innovation is a multiparticulate framework that empowers high medication stacking and is appropriate for products that

require granulation. This innovation comprises beads of controlled size and thickness utilizing granulation/ expulsion and spheronization strategies. It is an osmosis based system. The active pharmaceutical is kept in a reservoir surrounded by a semipermeable membrane laser drilled with a delivery orifice and formulated into a tablet. There are two layers in this tablet comprising of one drug layer and another osmotically active agent. Upon contact with gastrointestinal fluid, this osmotic agent changes its characteristic from non-dispensable to dispensable viscosity. Therefore active pharmaceutical is pushed away through the channel due to the pump effect of the osmotic agent. It is utilised generally for designing extended-release table.[6,35]

Contin® technology

This technology is Developed by Purdue Pharma provides for closer control over the amount of drug released to the bloodstream and benefits patients in terms of reducing the number of doses they need to take every day providing more effective control of their disease (particularly at night), and reducing unwanted side effects. In this technology, molecular coordination complexes are formed between a cellulose polymer and a nonpolar solid aliphatic alcohol optionally substituted with an aliphatic group by solvating the polymer with a volatile polar solvent and react the solvated cellulose polymer directly with the aliphatic alcohol, preferably as a melt. This constitutes the complex having utility as a matrix in controlled release formulations since it has a uniform porosity (semipermeable matrixes) which may be varied.[36, 33]

Diffutab® technology

Diffutab technology enables customized release profiles and region-specific delivery. Diffutab® technology uses a blend of hydrophilic and hydrophobic polymers to control drug release through diffusion through, and erosion of, a matrix tablet. Diffutab is particularly useful for high-dose products and drugs that require sustained release and/or once-a-day dosing.[13]

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. Skye Pharma 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.[26]

Oros®push pull innovation

This work on the principle of osmotic pressure to release the drug at a constant zero order rate.[37] This framework comprises principally a few layers among which at least one layer are fundamental to the medication and the other layer are comprised of the push layer. The medication layer basically comprises medication alongside at least two different agents. So this medication layer involves a drug that is poorly soluble in form. There is a further count of suspending agent and osmotic agent. A semi-permeable film covers the tablet centre.[38]

Sodas® (Spheroidal oral drug absorption system)

SODAS developed by ElanCorporation, is a Multiparticulate drug delivery system, consist of uniform spheroidal beads of 1-2mm in diameter. Each bead begins as an inert core onto which the drug is applied, followed by a number of layers of soluble and insoluble polymers combined with other excipients to produce the rate-controlling layer. Drug release from these beads occurs by a diffusion process. Within the GI tract, the soluble polymers dissolve, leaving pores within the outer membrane. The fluid then enters the core of the beads and dissolves the drug. The resultant solution diffuses out in a controlled, predetermined manner allowing for prolongation of the *in vivo* dissolution and absorption phases. The immediate environment of the drug within the seed core can be manipulated by the use of excipients to ensure optimal stability and solubility. These controlled-release beads can be packaged into a capsule or compressed into a tablet to produce the final dosage form. Based on the production of controlled release beads, the SODAS® technology is characterized by its inherent flexibility, enabling the production of customized dosage forms that respond directly to individual drug candidate needs.[39,40]

Intestinal Protective Drug Absorption System (IPDAS)

This innovative ion is 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 dispersesbeads containing a drug in the stomach, which is then 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/spheroid multiparticulates. The basic concept of IPDAS® was extended and modulated by Elan Drug Technology Company to formulate Naprelan®, which contains naproxen as the active ingredient.[41,42]

Chronotherapeutic oral drug absorption system (CODAS®)

Elan Drug technology developed CODAS® technology to achieve this prolonged interval. Many advantages of the CODAS® technology, including delivery profile

designed to complement circadian pattern, controlled onset, extended-release delivery system, rate of release essentially independent of pH, posture and food, "sprinkle" dosing by opening the capsule and sprinkling the contents on food, reduction in effective daily dose and drug exposure, gastrointestinal tract targeting for local effect and reduced systemic exposure to achieve a target profile.[34] This technology was applied on verapamil to produce a preparation named Verelan®PM taken at bedtime to be released 4-5 h after ingestion to target the highest blood pressure during the day, which is usually early morning. In order to achieve this delay in drug release, a combination of water-soluble and insoluble polymers was used to coat drug-loaded beads that were filled in a capsule. In the presence of GI fluids, the water-soluble polymers will dissolve gradually to form pores through which the active ingredient will be released over an extended period. The rate of verapamil release has been shown to be independent of pH, food and GI motility.[43]

Prodas Technology (Programmable oral drug absorption system)

PRODAS is a multiparticulate technology, which is unique in that it combines the benefits of tabletting technology within a capsule. PRODAS delivery system is presented as a number of minitablets combined in a hard gelatin capsule. The PRODOS technology can be used to pre-program the release rate of a drug. It is possible to incorporate many different minitablets, each one formulated individually, may be of different size and programmed to release drug at different sites within the gastrointestinal tract [44].

Egalet® technology

It is a delayed-release form consisting of an impermeable shell with two lag plugs, enclosing a plug of active drug in the middle of the unit. After the erosion of the inert plugs, the drug is released. Time taken to erode the inert plugs determines the lag time. The shells are made of slowly biodegradable polymers (e.g. ethylcellulose) and plasticizers (such as cetostearyl alcohol), while the matrix of the plugs is a mixture of pharmaceutical excipients including polymers like polyethylene oxide (PEO).[45]

timerx® technology

This innovation utilizes a blend of xanthan gum and locust bean gum blended in with dextrose. The actual collaboration between these segment attempts to shape a strong binding gel in presence of water. The arrival of medication is constrained by the rate of water penetration from GIT to the previously mentioned gum matrix, which grows to shape a gel and release a drug substance. The arrival of medication from a tablet can be controlled by changing the gum proportions, along with the third segment, the tablet covering and tablet producing measure. Possible use of this innovation is the improvement of oral, controlled release opioid pain-relieving oxymorphone.[46]

Three dimensional printing (3DP) technologies

It is used in the fabrication of complex oral dosage delivery pharmaceuticals based on solid free-form fabrication methods. It is possible to engineer devices with complicated internal geometries, varying densities, diffusivities, and chemicals. Different types of complex oral drug delivery devices have been fabricated using the 3DP process. The enteric dual pulsatile tablets were constructed of one continuous enteric excipient phase into which diclofenac sodium was printed into two separated areas. These samples showed two pulses of release in vitro with a lag time between pulses of about 4 hours. This technology is the basis of the TheirFORMs technology. The latter is a microfabrication process that works in a manner very similar to an ''inkjet'' printer. It is a fully integrated computer-aided development and manufacturing process. Products may be designed on a computer screen as three-dimensional models before actual implementation of their preparation process.[47]

Ceform™ technology

It allows the production of uniformly sized and shaped microspheres. This approach is based on ''melt-spinning'', which means subjecting solid feedstock (i.e., biodegradable polymer/bioactive agent combinations) to a combination of temperature, thermal gradients, mechanical forces, flow, and flow rates during processing. The microspheres obtained are almost perfectly spherical, having a diameter that is typically 150–180mm, and allow for high drug content. The microspheres can be used in a wide variety of dosage forms, including tablets, capsules, suspensions, effervescent tablets, and sachets. The microspheres may be coated for controlled release with an enteric coating or may be combined into a fast/slow release combination.[6]

Table 2: Marketed formulations.

TECHNOLOGY	MECHANISM	PROPRIETRY NAME	API	DISEASE	REFERENCE
OROS®	Osmotic system	Covera-HS®;XL tablet	Verapamil HCl	Hypertension	[48]
OROS®	Osmotic system	Invega™	Paliperidone	Schizophrenia	[46]
Pulsincap™	Rupturable system	Pulsincap™	Dofetilide	Hypertension	[10]
CODAS	Multi particulate pH dependent system	Veralan PM;XL release capsule	Verapamil HCl	Hypertension	[49]
3D Printing	Externally regulated system	Their Form	Diclofenac sodium	Inflammation	[50]
DIFFUCAPS®	Multiparticulate system	Innopran®; XL Tablets	Verapamil Hcl, Propranolol Hcl	Hypertension	[51]
TIMERx®	Erodible/soluble barrier coating	OPANA® ER tablets	Oxymorphone	Pain management	[16]
CONTIN®	Extended release tablet	Uniphyl®	Theophylline	Asthma	[46]
PULSYS™	Multiparticulatesystem	Moxatag™	Amoxicilline	infection	[9]

Table 3: Patents related to pulsatile drug delivery system.

Patent number	Technology	Api	Date of patent	Reference
Us5213808	Multi-layered article	Captopril	May25,1993	[52]
Us5312325	Pulsating transdermal technology	Nitroglycerine	May 17,1994	[53]
Us 5834023	Pulsatile technology	Dilitazemhcl.	Nov.10,1998	[54]
Us 6217904	Pulsatile technology	Methylphenidate	Apr.17,2001	[55]
Us 6322819	Oral pulsatile technology	Amphetamine	Nov.27,2001	[56]
Us6605300	Oral pulsatile technology	Amphetamine	Aug.12,2003	[57]
Us 6635277	Pulsatile technology	Dilitazem hcl	Oct. 21,2003	[58]
Us 7048945	Time controlled drug delivery method	Sotalol hcl	May23,2006	[59]

CONCLUSIONS

The timing of drug administration in disease therapy has a major impact on treatment success. As discussed in the article pulsatile drug delivery system delivers the medication at the right time, right place in the right amount holds beneficial ways for the treatment of various diseases. This therapy is mainly applicable where sustained action is not required and drugs are toxic. Now various FDA approved chronotherapeutic drugs are available in the market which surely assures a bright and promising future.

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