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Review Article

CURRENT TECHNIQUES IN PULSATILE DRUG DELIVERY: A REVIEW

RajkumarKotha*[1], Sainath Goud Raghavapally[2], Suryasri Lavanya Adavi[1], Sangamesh Taranalli[1], Dibya Pandey[1]
[1]Department of Pharmaceutics, KLEU's College of Pharmacy, JNMC Campus, Belgaum, Karnataka, India
[2]Department of Pharmaceutics, Sri Venkateshwara College of Pharmacy, Madhapur, Hyderabad, Andhrapradesh, India
Email: rajkumar10885@gmail.com

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ABSTRACT
The purpose of writing this review on pulsatile drug delivery system (PDDS) is to compile the recent literatures with special focus on the different types and approaches involved in the development of the formulation and classification, advantages, limitation, and future aspects of pulsatile drug delivery system. PDDS is gaining a lot of interest as they deliver the drug at the right place at the right time and in the right amount, thus providing spatial and temporal delivery and increasing patient compliance. These systems are designed according to the circadian rhythm of the body. The principle rationale 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 a lag time. In this article, various systems like capsular systems, osmotic systems, single and multiple-unit systems based on the use of soluble or erodible polymer coating and use of rupturable membranes have been dealt. It summarizes the latest technological developments (including Wirelessly Controlled Drug-delivery MicroChip), formulation parameters, and release profiles of these systems.
Key Words: Pulsatile Drug Delivery System, Osmotic Systems, Circadian rhythm, Temporal delivery, MicroChip

INTRODUCTION

Modified release dosage forms have acquired a great importance in the delivery of drugs in various diseases. Such systems offer control over the release pattern of drug and provide better control over drug regimen. Such systems release the drug with predetermined release rates, either constant or variable. These dosage forms offer numerous advantages, such as nearly stable plasma drug level without much fluctuation, reduction in dose of drug, reduced dosage frequency, least side effects, and improved patient compliance[1]. It is well documented that most of the body functions like heart rate, stroke volume, blood pressure, blood flow, body temperature, gastric pH display circadian rhythms. Moreover, in a number of organs their functions vary with the time of the day. It is increasingly recognized that there are rhythmic and temporal patterns in the manifestation of many disease states.

Traditionally drugs are released in an immediate or extended pattern. However in recent years, pulsatile release systems are gaining growing interest, where the drug is released rapidly after a well defined lag time (Lag time is defined as the time between when a dosage form is placed into an aqueous environment and the time at which the active ingredient begins to get released from the dosage form (Ayres, 2004)), could be adventitious for many drugs or therapies. Pulsatile drug delivery is one that releases a therapeutic agent at a rhythm that ideally matches biological requirement of a given disease therapy[2].

In these systems, there is rapid and transient release of a certain amount of drug molecules within a short time period immediately after a predetermined off release period, i.e. lag time (Survase & Kumar, 2007). Various techniques are available for the pulsatile delivery like pH dependent systems, time dependent systems, microflora activated systems etc. which can be designed as per the physiology of disease and properties of the drug molecule (Survase & Kumar, 2007)[3].

The pulsatile effect, i.e., the release of drug as a "pulse" after a lag time has to be designed in such a way that a complete and rapid drug release should follow the lag time [4,5]. Such systems are also called time-controlled as the drug released is independent of the environment. Pulsatile drug delivery systems are gaining a lot of interest and attention these days.

Table 1: Diseases requiring Pulsatile drug delivery

Disease	Chronological Behavior	Drugs
Cardiovascular diseases	BP is at its lowest during the sleep cycle and rises steeply during the early morning period.	β Blockers, ACE inhibitors, ARBs (Angiotensin receptor blockers), Calcium channel blockers etc.
Asthma	Precipitation of attacks during night or at early morning hours.	β_2 agonists (e.g. salbutamol, salmeterol etc.) and Antihistamines (e.g.Hydroxazine, L-cetrizine etc.)
Arthritis	Pain in the morning and increased pain at night.	NSAIDs, Glucocorticoids
Attention deficit syndrome	Increase in DOPA level in the afternoons.	Methylphenidate and Atomoxetine.
Diabetes mellitus	Increase in the blood sugar level after meals.	Sulfonylureas, Insulin, Biguanides
Hypercholesterolemia	Cholesterol synthesis is generally higher during night than during day time.	HMG CoA reductase inhibitors
Peptic ulcer	Acid secretion is high in the afternoon and at nights.	H_2 blockers (e.g. Ranitidine, nizatidine, famotidine etc.)

Advantages of Pulsatile drug delivery: [6]

- Extended daytime or night time activity.
- Reduced side effects.
- Reduced dosage frequency.
- Reduction in dose size.

- Improved patient compliance.
- Lower daily cost to patients as fewer dosage units are required by the patient during therapy.
- Drug targeting to specific sites like colon.
- Protection of mucosa from irritant drugs.
- Drug loss is prevented from first pass effect.
- Predictable, reproducible and short gastric residence time.
- Less inter and intra-subject variability.
- Improved bioavailability.
- Limited risk of local irritation.
- No risk of dose dumping.
- Flexibility in design.
- Improved stability.
- Drug adapts to suit circadian rhythms of body functions or diseases.

Disadvantages [7]

- Lack of manufacturing reproducibility and efficacy.
- Large number of process variables.
- Higher cost of production.
- Trained/skilled personnel needed for manufacturing.
- Unpredictable IVTVC.

Classification of Pulsatile drug delivery systems

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. Magnetically induced pulsatile release.
  B. Ultrasound induces release.
  C. Electro responsive pulsatile release.
  D. Light induces release.
IV. Pulsatile release systems for vaccine and hormone products.
V. Sigmoidal Release System.

Time Controlled Pulsatile Release

In time controlled drug delivery system, drug is released in pulsatile manner after a specific time interval in order to deliver the drug to the desired site at the required time, thus mimicking the circadian rhythm[8].

Single Unit System

Pulsatile delivery by solubilisation or erosion of layer

In such systems, the core containing drug is coated with the soluble or erodible polymer as outer coat and drug release is controlled by the dissolution or erosion of the outer coat[9]. Time dependent release of the drug can be obtained by optimizing the thickness of the outer coat as shown in Figure 1.

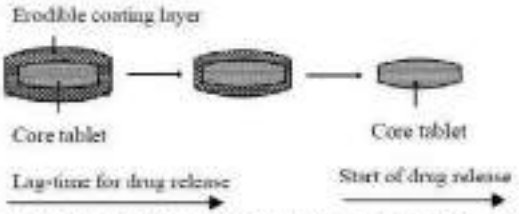

Figure 1: schematic diagram of drug delivery with erodible coating layer

Pulsatile delivery by rupture of membrane

Instead of swelling or erosion, these systems are dependent on the disintegration of the coating for the release of drug. The pressure necessary for the rupture of the coating can[10] be achieved by the swelling, disintegrants, effervescent excipients, or osmotic pressure. Water permeation and mechanical resistance of the outer membrane are major factors affecting the lag time. Figure 2 shown drug delivery with rupturable coating layer

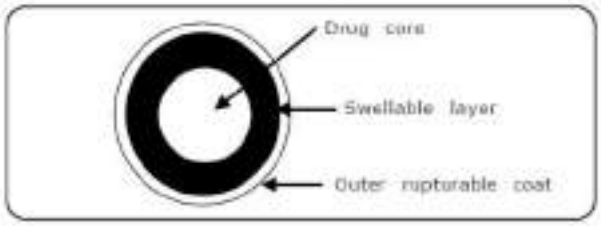

Figure 2: Schematic diagram of drug delivery with Rupturable coating layer

Capsule Shaped Pulsatile Drug Delivery System

This dosage form consists of an insoluble capsule body containing a drug and swellable and degradable plugs made of approved substances such as hydrophilic polymers or lipids and release controlling plug between immediate release compartment and pulsed release compartment. On contact with aqueous fluids, the cap rapidly dissolves thereby releasing the immediate release component followed by pulsed release component. The length of plug decides lag time[11,12]. The release of drug from capsule shown in Figure 3.

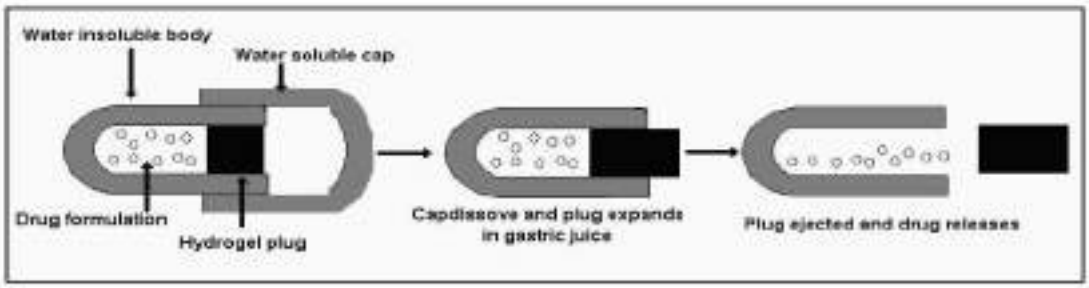

Figure 3: Schematic diagram of release of drug from capsule

Pulsatile system based on osmosis

Osmotic system consists of capsule coated with the semi-permeable membrane. Inside the capsule there is an insoluble plug consisting of osmotically active agent and the drug formulation[13]. e.g. The Port® System (Figure 4)

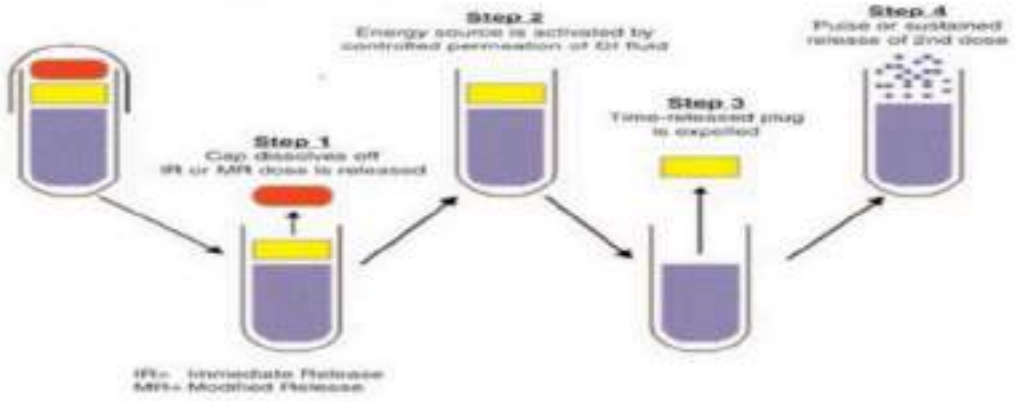

Figure 4: Schematic diagram of osmosis system (The port system)

Multipaticulate System

Recent trends indicate that multi-particulate drug delivery systems are especially suitable for achieving controlled or delayed release of oral formulations with low risk of dose dumping, flexibility of blending to attain different release patterns as well as reproducible and short gastric residence time. Such systems are reservoir type with either rupturable or altered permeability coating and generally housed in capsular body. The purpose of designing multi-particulate dosage form is to develop a reliable formulation that has all the advantages of a single unit formulation and yet devoid of the danger of alteration in drug release profile and formulation behaviour due to unit to unit variation[14] Hypothetical design of a multiparticulate pulsatile system is shown in Figure 5.

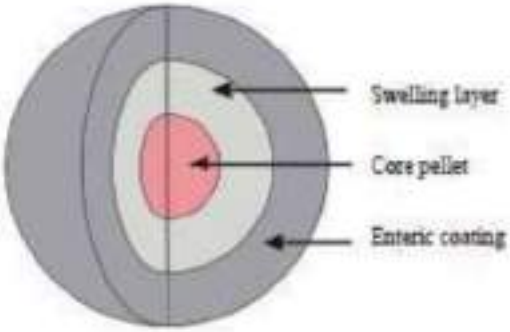

Figure 5: Hypothetical design of a Multiparticulate pulsatile system

Andrei Dashevsky, et al. developed a pulsatile multiparticulate drug delivery system (DDS), coated with aqueous dispersion of Aquacoat® ECD. A rupturable pulsatile drug delivery system consists of (i) a drug core; (ii) a swelling layer, comprising a superdisintegrant and a binder; and (iii) an insoluble, water-permeable polymeric coating[15]. Upon water ingress, the swellable layer expands, resulting in the rupturing of outer membrane with subsequent rapid drug release. The lag time was shorter in the theophylline cores layered with sugar when compared to the cores of uncoated theophylline. In case of the swelling layer, the release after lag time was fast and complete. Drug release was achieved after the lag time, when low-substituted hydroxypropyl cellulose (L-HPC) and sodium starch glycolate (Explotab®) were used as swelling agents. Outer membrane, formed using aqueous dispersion Aquacoat® ECD was brittle and ruptured sufficiently to ensure fast drug release, compared to ethylcellulose membrane formed using organic solution. The addition of talc led to increase brittleness of membrane and was very advantageous. Drug release starts only after rupturing of outer membrane.

C. Sun, et al. developed novel pH sensitive copolymer microspheres containing methylacrylic acid and styrene cross-linking with divinyl benzene were synthesized by free radical polymerization. The copolymer microspheres showed pulsatile swelling behaviour when the pH of the media changed. The pH sensitive microspheres were loaded with diltiazem hydrochloride (DH)[16]. The release characteristics of the free drug and the drug-loaded microspheres were studied under both simulated gastric conditions and intestinal pH conditions. The in *vivo*-evaluation of the pulsatile preparation was subsequently carried out using beagle dogs.

Stimuli Induced Pulsatile Release System

Several polymeric delivery systems undergo phase transitions and demonstrate marked swelling and deswelling changes in response to environmental changes including solvent composition, ionic strength, temperature, electric fields, and light[17].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 synergies 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 [18]

Thermo-Responsive Pulsatile Release

Temperature Induced Pulsatile Release

This deviation sometimes can act as a stimulus that triggers the release of therapeutic agents from several temperature responsive drug delivery systems for diseases accompanying fever. The temperature induced pulsatile/triggered drug delivery systems utilize various polymer properties, including the thermally reversible coil/globule transition of polymer

molecules, swelling change of networks, glass transition and crystalline melting[20-24].

Thermoresponsive Hydrogel Systems

Thermo-responsive hydrogel systems employ hydrogels which undergo reversible volume changes in response to changes in temperature. These gels shrink at a transition temperature that is referred to the lower critical solution temperature (LCST) of the linear polymer. Thermo-sensitive hydro-sensitive hydrogels have a certain chemical attraction for water, and therefore they absorb water and swell at temperatures below the transition temperature whereas they shrink or deswell at temperatures above the transition temperature by expelling water. Thermally responsive hydrogels and membranes have been extensively exploited as platforms for the pulsatile drug delivery[25].

Thermo Responsive Polymeric Micelle Systems

In this type, the gel system tightly stores targeted drug in the micelles and rapidly releases controlled amount of the drug by switching on–off of external stimuli such as temperature or infrared laser beam. Jianxiang Zhang, et al synthesized thermally responsive amphiphilic poly(Nisopropylacrylamide) (PNIPAm)-graftedpoly phosphazene(PNIPAm-g- PPP) by stepwise cosubstitution of chlorine atoms on polymer backbones with amino-terminated NIPAm oligomers and ethyl glycinate(GlyEt)[26]. Diflunisal (DIF)-loaded micelles were prepared by dialysis method. *In vitro* release test at various temperatures was also performed to study the effect of temperature on the drug release profiles.

Chemical stimulion 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. 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, polyoletc[27,28].

Inflammation-Induced Pulsatile Release

On receiving any physical or chemical stress, such as injury, fracture etc., inflammation takes 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[29].

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.

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 changes 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 carboxy methyl cellulose. These polymers are used as enteric coating materials so as to provide release of drug in the small intestine [30].

Enzymatically-Activated Liposome

Drug loaded liposomes was incorporated into microcapsules of alginate hydrogels. Liposomes inside the microcapsules were coated with phospholipase A2 to achieve a pulsatile release of drug molecules. Phospholipase A2 was shown to accumulate at the water/liposome interfaces and remove an acyl group from the phospholipids in the liposome. Destabilised liposomes release their drug molecules, thus allowing drug release to be regulated by the rate determining microcapsule membrane [31, 32].

Externally Regulated Pulsatile Release system

This system is not self-operated, but instead requires externally generated environmental changes to initiate drug delivery. These can include magnetic fields, ultrasound, electric field, light, and mechanical force.

Magnetic Induces Release

Magnetic carriers receive their magnetic response to a magnetic field from incorporated materials such as magnetite, iron, nickel, cobalt etc. Magnetic-sensitive behaviour of intelligent Ferro gels for controlled release of drug was studied by Tingyu Liu, et al. An intelligent magnetic hydrogel (ferrogel) was fabricated by mixing poly (vinyl alcohol)(PVA) hydrogels and Fe3O4 magnetic particles through freezing-thawing Cycles[33]. Although the external direct current magnetic field was applied to the ferrogel, the drug got accumulated around the ferrogel, but the accumulated drug spurt to the environment instantly when the magnetic fields instantly switched "off". Furthermore, rapid slow drug release can be tunable while the magnetic field was switched from "off" to "on" mode. The drug release behaviour from the ferrogel is strongly dominated by the particle size of Fe_3O_4 under a given magnetic field[34]. Tingyu Liu, et al developed the magnetic hydrogels which was successfully fabricated by chemically cross linking of

gelatine hydrogels and Fe_3O_4 nanoparticles (40–60 nm) through genipin (GP) as cross linking agent[35].

Ultrasound Induces Release

Ultrasound is mostly used as an enhancer for the improvement of drug permeation through biological barriers, such as skin. The interactions of ultra sound with biological tissues are divided into two broad categories: thermal and non thermal effects. Thermal effects are associated with the absorption of acoustic energy by the fluids ortissues[36]. Non-thermal bio-effects are generally associated with oscillating or cavitating bubbles, but also include non cavitation effects such as radiation pressure, radiation torque, and acoustic streaming.

Electric Field Induces Release

Electrically responsive delivery systems are prepared by polyelectrolyte's (polymers which contain relatively high concentration of ionisable groups along the backbone chain) and are thus, pH-responsive as well as electro-responsive. Under the influence of electric field, electro-responsive hydrogels generally bend, depending on the shape of the gel which lies parallel to the electrodes whereas deswelling occurs when the hydrogel lies perpendicular to the electrodes. An electro-responsive drug delivery system was developed by R. V. Kulkarni, et al., using poly (acrylamide-grafted-xanthan gum) (PAAm-g- XG) hydrogel for transdermal delivery of ketoprofen.[37]

Light Induces Release

Light-sensitive hydrogels have potential applications in developing optical switches, display units, and opthalmic drug delivery devices[38]. The interaction between light and material can be used to modulate drug delivery. When hydrogel absorb the light and convert it to heat, raising the temperature of composite hydrogel above its LCST1, hydrogel collapses and result in an increased rate of release of soluble drug held within the matrix.

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 [39]. 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[40]. 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.

Sigmoidal Release System

This consists of pellet cores containing drug and succinic acid coated with ammonio methacrylate copolymer USP/NF type B. The lag time is controlled by the rate of water influx through the polymer membrane. The water dissolves succinic acid, and the drug in the core and the acid solution in turn increases permeability of the hydrated polymer film. In addition to succinic acid, acetic acid, glutaric acid, tartaric acid, malicacid, or citric acid can be used. The increased permeability can be explained by improved hydration of film, which increases free volume. These findings were used to design a coated delivery system with an acid-containing core[41, 42]. The in-vitro lag time correlated well with in-vivo data when tested in beagle dogs.

Recent advances in Oral Pulsatile Delivery Technology[32]

ACCU-BREAK Technology

ACCU-BREAK tablets are designed to provide physicians and patients with easily divisible tablets that when divided, result in exact smaller doses, thus facilitating ease of dosage adjustment. In ACCU-T-CR Trilayer tablets, the controlled release technology is used to further enhance treatment options. Tablet contains a controlled-release (CR) medication at either end separated by a drug-free break layer, allowing the CR dose to be divided into exact half doses. Additionally, an immediate release (IR) component can be added to CR tablets to add even more treatment options and potential product capabilities [44].

SODAS Technology

Spheroidal Oral Drug Absorption System is Elan's Multi particulate drug delivery system. 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. The system consists of uniform spheroidal beads of 1-2mm in diameter containing drug & excipients and is coated with product specific controlled release polymers.

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[49].

IPDAS Technology

The Intestinal Protective Drug Absorption System is intended for use with GI irritant compounds. This is a high density, multi particulate tablet technology used for the manufacture of Naproxen. 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.

CODAS Technology

The Chronotherapeutic Oral Drug Absorption System is developed to achieve delay in drug action. This system is tailored to release drug after a pre-determined delay, a drug release profile which complements the circadian rhythms or patterns is obtained. E.g. Verapamil is formulated as VERELAN [48]. The drug is released 4-5 hours after ingestion; the delay is achieved by polymer coatings to the drug loaded beads. This drug is used in the treatment of arrhythmias. When taken at bed time, it ensures that a maximum plasma concentration is obtained in the morning hours when the symptoms of cardiac arrythmias worsen [33].

PRODAS Technology

Programmable Oral Drug Absorption System is a multi particulate technology which combines the benefits of tableting technology within a capsule. Here, the release rate of the drug can be pre-programmed. In this technology, it is possible to incorporate many different minitablets, each one formulated individually and programmed to release drug at different sites within the gastro-intestinal tract. It is also possible to incorporate minitablets of different sizes so that high drug loading is possible.

TMDS Technology

The Time Multiple Action Delivery System provides controlled release rate of multiple ingredients within a single tablet.

DMDS Technology

The Dividable Multiple Action Delivery System technology is designed to provide greater dosing flexibility which improves product efficacy and reduces side effects. This technology allows the tablet to be broken down into half so that each respective portion of the tablet will achieve exactly the same release rate profile as that of the tablet, hence, dosage regimens can be adjusted easily.

PMDS Technology

The Programmable Multiple Action Delivery System technology enables the active ingredient to be delivered in a more controlled fashion. This technology provides greater dosing flexibility that may improve or reduce the product efficacy. This technology allows us to overcome one of the technical challenges in the development of multi-particulate dosage forms achieving acceptable uniformity and reproducibility of a product with a variety of release rates.

GEOCLOCK Technology

This technology involves chronotherapy focused press-coated tablets which contain 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 [45].

E.g. LODOTRA – used in rheumatoid arthritis, is formulated by this technology.

Geomatrix Technology

This technology enables the simultaneous release of two different drugs and at different rates from a single tablet. This is achieved by constructing a multilayered tablet. The combination of layers, each with different rates of swelling, erosion is responsible for the rate of drug release within the body [45].

PULSYS Technology

This technology is used for once daily pulsatile dosing. A compressed tablet that contains pellets designed to release drug at different regions in the GI tract in a pulsatile manner is prepared.

E.g. Amoxicillin is formulated in this way, and showed improved bactericidal action.

OSDRC Technology

One Step Dry Coating technology is a unique, innovative, low cost and high quality technology. The OSDrC rotary tabletting machine has a variable double punch configuration which allows production of tablet within a tablet (cored tablets) [46].

Intellimatrix Technology

Contains a unique composition of several different intelligent polymers such as HEC and a channel former as lactose. This system enables precise profile control and site specific drug delivery [47].

EURAND'S Pulsatile and Chrono release system

This system can provide one or more rapid release pulses at predetermined lag times. 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. For e.g, Propranolol HCl is formulated as this system and is used in the treatment of cardiovascular diseases. When administered at bed time, the drug is released after an initial delay such that maximum plasma concentration levels occur in the early morning hours, when the patient is more at risk.

EURAND'S Diffucap Multi Particulate System

This system is created by first layering active drug onto an inner core made up of sugar/cellulose spheres, and then applying one or more rate controlling, functional polymers so as to produce spherical multilayered particles.

E.g. Innopran is a diffucap formulation containing propranolol and verapamil which are released approximately 4-5 hours after ingestion. The delay is introduced by the level of release controlling polymer applied to the drug loaded beads.

Diffutab Technology

This technology is useful for sustained and targeted pulsed delivery. This system incorporates a blend of hydrophilic polymers that control drug release via diffusion and erosion of a matrix tablet.

Orbexa Technology

This is a multi particulate system that enables high drug loading and provides a formulation choice for products that require granulation .After spheronization, the resultant beads can be coated with functional polymer membranes for additional release rate control and may be filled into capsules. This technology can be used for sensitive drugs such as proteins.

EURAND'S Minitabs Technology

This technology combines the simplicity of tablet formulation with the sophisticated drug release control offered by multi particulate systems. These minitabs are tiny (approx. 2 mm in diameter) cylindrical tablets.[48] Coating membranes can be applied to the tablets to control release rate.

BANNER'S Versetrol Technology

This technology is a novel innovative technology that provides time controlled release for wide range of drug. Here, the drug is incorporated in lipophilic or hydrophilic matrix which is then incorporated in soft gelatin capsule shell. This technology is versatile because, depending on physiochemical properties of drug, either emulsion or suspension can be developed. For lipophilic drugs, suspension formulation is preferred, while for hydrophilic drugs emulsion form is utilized. By applying combination of lipophilic and hydrophilic matrices desire release profile can be achieved.

Magnetic Nanocomposite Hydrogel

Magnetic nano-composite was synthesized by incorporation of super paramagnetic Ferric oxide particles in temperature sensitive poly (Nisopropylacrylamide) 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.

Wire-Less Controlled Drug Delivery Chip

MIT professors Robert Langer and Michael Cima reported that they have successfully used MicroCHIPS to administer daily doses of an osteoporosis drug normally given by injection.

In the new study, funded and overseen by MicroCHIPS, scientists used the programmable implants to deliver an osteoporosis drug called teriparatide to seven women aged 65 to 70. The study found that the device delivered dosages comparable to injections, and there were no adverse side effects.

These programmable chips could dramatically change treatment not only for osteoporosis, but also for many other diseases, including cancer and multiple sclerosis. Patients with chronic diseases, regular pain-management needs or other conditions that require frequent or daily injections could benefit from this technology.

Marketed Products

Technology	Mechanism	API	Disease
Pulsys®	Timed-controlled system	Amoxicillin	Pharyngitis/tonsillitis
Uniphyl®	Externally regulated system	Theophylline	Asthma
Ritalina®	Osmatically regulated	methylphenidate	Attention Deficit Hyperactive Disorder (ADHD) - in children
Opana® ER	Timed-controlled system	Oxymorphone	Pain medicine
TheirForm®	Externally regulated system	Diclofenac	Inflammation

CONCLUSION

From the above review, it can be concluded that 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 chrono-pharmacotherapy. Therefore, Circadian rhythm of the body is an important concept for understanding the optimum need of drug in the body. As there is a constant need for new delivery systems that can provide increased therapeutic benefits to the patients, Pulsatile drug delivery, one such system that, by delivering drug at the right time, right place and in right amounts, holds good promises of benefit to the patients suffering from chronic problems like arthritis, asthma, hypertension etc.

Abbreviations: Pulsatile Drug Delivery System (PDDS)

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