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Pulsatile Drug Delivery System: Current scenario

Jyothi. M*[1], Kavitha.K[1], M.Rupesh Kumar[1], Jagadeesh Singh[1], N.Sunil[1], Santosh[1],
1. East Point College of Pharmacy, Bangalore – 560 049, Karnataka, India.

ABSTRACT

Conventionally, drugs are released in an instant or absolute manner. Nevertheless, in current days, Pulsatile Drug Release Systems (PDRS) are gaining upward attention. Pulsatile delivery is defined as the rapid and transient release of certain amounts of drug molecules within a short time period immediately after a predetermined off-release period, i.e., lag time. PDRS can be classified in single and multiple pulse systems. This system provides spatial and temporal delivery of the drug. These systems are designed according to the circadian rhythm or biological clock of the body. These deliver the drug at the right time and at the right place and in the right amount thus increasing patient compliance. Pulsatile systems are beneficial for drugs where night time dosing is required, such as anti-asthmatic and anti-arrhythmic drugs where the disease severity is time dependent. This concept has several advantages, notably maximum therapeutic benefit, minimum harm, improved patient convenience and compliance. Pharmacists must realize the need to develop and dispense such medications having potential therapeutic benefit. The current article focuses on the diseases requiring PDDS, methodologies involved for the existing systems, and PDDS product currently available in the market.

Keywords: Chronopharmacological, Port System, Pulsincap system, osmotic pumps.

*Corresponding Author Email: jyothim.pharmacy@gmail.com
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INTRODUCTION

With the advancement of the pharmaceutical field, novel drug delivery systems have drawn an increasing attention in the last few decades. Now, 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 [1-2]. Oral controlled release drug delivery systems are designed to deliver the drugs at a controlled and predetermined rate thus maintaining their therapeutically effective concentration in systemic circulation for prolonged periods. On the other hand, for certain therapies a pulsatile drug release pattern, where the drug is released after well-defined lag time, exhibits significant advantages[3]. In humans, circadian rhythm regulates various body functions like metabolism, physiology, behavior, sleep patterns and hormone production. It has been reported that more shocks and heart attacks occur during morning hours. The number of hormones like rennin, aldosterone, and cortisol show daily fluctuations in their blood levels[4]. Pulsatile drug delivery system has gained increasing importance not just for the treatment of diseases that are influenced by the circadian rhythm of the body, but also for the potential it holds to prevent the down regulation of drug receptors and to achieve efficient therapeutic effects. Pulsatile drug delivery systems release active ingredient completely and rapidly after a defined lag time, Such systems are advantageous for: (i) Drugs with an extensive first pass metabolism and developed biological tolerance, (ii) the targeting of locally absorbed or acting drugs to a specific site in the intestinal tract, and (iii) the adaptation of the therapy to chronopharmacological needs[5].Colon delivery is being extensively investigated as it may yield improved topical inflammatory bowel disease (IBD) treatments and is even suggested as one means of enhancing the poor oral bioavailability of peptides, proteins, oligonucleotides and nucleic acids[6].

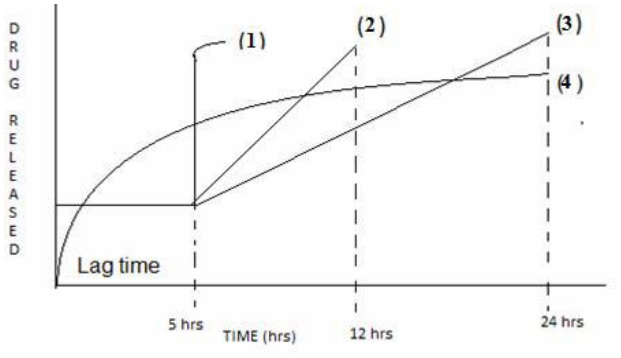

Figure 1: Schematic representation of different drug delivery systems where (1) sigmoidal release after lag time (2) delayed release after lag time (3) sustained release after lag time (4) extended release without lag time [53] .

Table 1: Diseases requiring Pulsatile Drug Delivery [55].

Disease	Chronological behavior	Drugs used
Peptic ulcer	Acid secretion is high in the afternoon and at night	H2 blockers
Asthma	Precipitation of attacks during night or at early morning hour	β_2 agonist, Antihistaminics
Cardiovascular diseases	BP is at its lowest during the sleep cycle and rises steeply during the early morning awakening period	Nitroglycerin, Calcium channel blocker, ACE inhibitors etc.
Arthritis	Pain in the morning and more pain at night	NSAIDs, Glucocorticoids
Diabetes mellitus	Increase in the blood sugar level after meal	Sulfonylurea, Insulin, Biguanide
Attention deficit syndrome	Increase in DOPA level in afternoon	Methylphenidate
Hypercholesterolemia	Cholesterol synthesis is generally higher during night than during day time	HMG CoA reductase inhibitors
Neoplastic	It has been demonstrated that "Susceptibility rhythms" to drugs may differ between healthy tissue and cancerous tissue.	Antimetabolites, Alkylating agents, Vinca alkaloids, antibiotics etc.

The principle rationale for the use of pulsatile release is for the drugs where a constant drug release, i.e., a zero-order release is not desired[7]. Pulsatile drug delivery systems are generally classified into time-controlled and site-specific delivery systems. The release from the first group is primarily controlled by the system, while the release from the second group is primarily controlled by the biological environment in the gastro-intestinal tract such as pH or enzymes[8].

Methodologies for PDDS:

I. Time Controlled Pulsatile Drug Delivery:

In this system pulsatile release is obtained after a particular time interval in order to mimic the circadian rhythm. Such type of pulsatile drug delivery system contains two gears: one is of immediate release type and other one is a pulsed release type [9]. Most delayed release delivery systems are reservoir devices covered with a barrier coating, which dissolves, erodes or ruptures after a lag phase. Well-known coating technique employs a water-permeable but insoluble film which encloses the active ingredient and an osmotic agent and it may be adjusted for selecting suitable rates of water permeation, and thereby, release time. Water from the gut slowly diffuses through the film into the core and swells until the film burst, releasing the drug [10].

A. Single unit pulsatile systems:

1.Capsular based systems

Capsular systems are generally comprised of "Pulsincap system", which consists of an insoluble capsule body, swellable and degradable plugs made of approved substances such as hydrophilic polymers and lipids and bioactive molecule. The lag time is controlled by plug, which is pushed away by swelling or erosion and drug is released as a pulse from the insoluble capsule i.e. Pulsincap. A swellable hydrogel seals the drug contents into the capsule body. When this capsule body comes in contact of dissolution medium, the hydrogel plug swells and after a lag time, the plug pushes itself outside the capsule and rapidly releases the drug. The polymers generally used for plugs include hydroxyl propyl cellulose, poly vinyl acetate, polyethylene-oxide etc. The swelling strength of plug decides the lag time[11].

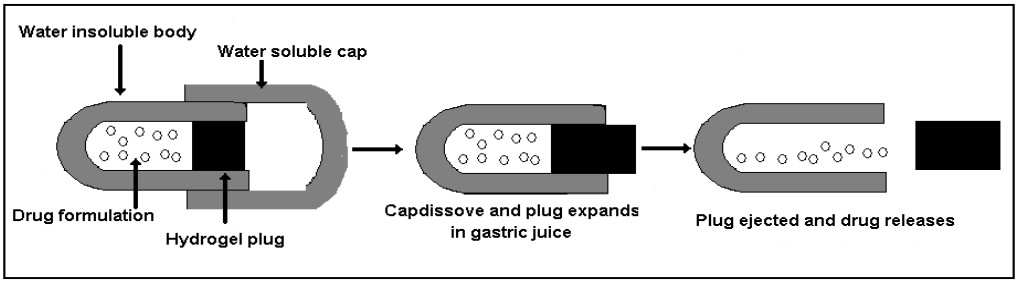

Figure 2: Drug Release Mechanism In Pulsincap® System [23].

2.Capsular Based On Osmosis:

PORT systems

This system consists of a capsule coated with a semi permeable membrane. Inside the capsule was an insoluble plug consisting of osmotically active agent and the drug Formulation e.g.: Port® System Osmotic delivery capsules ("osmotic pumps") function by virtue of walls which selectively pass water into the capsule reservoir. Absorption of water by the capsule through these walls is driven by a water-attracting agent in the capsule interior which creates osmotic pressure across the capsule wall. The water-attracting agent may be the beneficial agent itself whose controlled release is sought, but in most cases, it is a separate agent specifically selected for its ability to draw water, and this separate agent is being isolated from the beneficial agent at one end of the capsule. The pulsatile effect of a drug is achieved by combining the drug with a modulating agent. The modulating agent is selected on the basis of its solubi1ity in the delivery medium relative to the beneficial agent and the pulsatile effect results from one of the two agents falling below its saturation point, causing go into solution and released[13].The lag time is controlled by the thickness of the coating. E.g. Ritalin (methyl phenidate) used in the treatment of attention deficit hyper active disorder (ADHD) in children, is formulated as PORT system. The use of this system avoided second time dosing which is beneficial for school children [13].

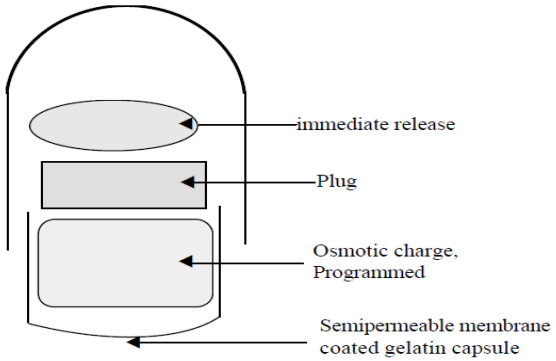

Figure 3: Schematic Diagram Of Osmosis System [54].

System based on Expandable orifice

The delivery of the drug was driven by the osmotic infusion of the moisture by the capsule from a physiological environment. The capsule wall is made up of an elastic material and possesses an orifice. As the osmosis proceeds, the pressure within the capsule rises which causes the wall to stretch. The orifice is small enough so that when the elastic wall relaxes, the flow of the drug through the orifice essentially stops, but when the elastic wall is distended beyond threshold value, the orifice expands sufficiently to allow drug release at a required rate. Uses of elastomers, such as styrene butadiene copolymer have been reported. Lag times can be modified by changing the thickness of the barrier layer and that of semipermeable membrane. Pulsatile release was achieved after lag times of 1 to 10 hours, depending on the thickness of the barrier layer and that of semipermeable membrane, and a capsule designed for implantation can deliver drug intermittently at intervals of 6 hours for 2 days [14].

Delivery by series of stop

This system is described for implantable capsules. The capsule contains a drug and a water-absorptive osmotic engine that are placed in compartments separated by a movable partition. The pulsatile delivery is achieved by a series of stops along the inner wall of the capsule. These stops obstruct the movement of the partition but are overcome in succession as the osmotic pressure rises above a threshold level. The number of stops and the longitudinal placements of the stops along the length of the capsule dictate the number and frequency of the pulses, and the configuration of the partition controls the pulse intensity. This system was used to deliver porcine somatotropin [15].

Pulsatile delivery by solubility modulation

These systems contain a solubility modulator for pulsed delivery of variety of drugs. The system was especially developed for delivery of antiasthamatic drug; salbutamol sulphate[16].The

compositions contain the drug (salbutamol sulphate) and a modulating agent (sodium chloride). The amount of sodium chloride was such that it was less than the amount needed to maintain saturation in a fluid that enters the osmotic device. The pulsed delivery is based on drug solubility. Salbutamol has solubility of 275 mg/ml in water and 16 mg/ml in saturated solution of sodium chloride, while sodium chloride has solubility of 321 mg/ml in water, and its saturation solubility is 320 mg/ml. These values show that the solubility of the drug is dependent on the modulator concentration, while the modulator's solubility is largely independent of drug concentration. The modulating agent can be a solid either organic acid or inorganic/organic salt. By changing the ratio of drug/modulator, zero-order release period and commencement of pulsed release can be controlled. After the period of zero-order release, the drug is delivered as one large pulse. A similar system is described for delivery of terbutaline and oxprenolol[17].

3. Pulsatile system with Erodible or soluble barrier coatings:

This system consists of a reservoir device coated with a barrier layer. The barrier dissolves after a specific lag time, after that the drug is released rapidly. The lag time depends on the thickness of the coating layer. This system consists of a solid dosage form coated with lipidic barriers containing carnauba wax and bees wax along with surfactants (spans). After a lag time proportional to the thickness of the film, the coat erodes or emulsifies in the aqueous environment and then the core is available for Dispersion [18].

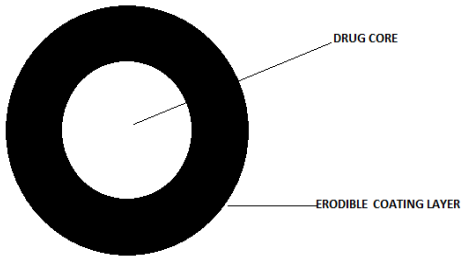

Figure 4: Schematic Diagram of Delivery Systems with Erodible Coating Layers [9].

The chronotropic system

The Chronotropic® system consists of a drug containing core coated by hydroxypropylmethyl cellulose (HPMC), a hydrophilic swellable polymer, which is responsible for a lag phase in the onset of release[19]. In addition, by coating the system by enteric polymer such as cellulose acetate phthalate, the variability in gastric emptying time can be overcome, and a colon-specific release can be obtained, assuming small intestinal transit time is not changed[20]. The lag time is controlled by the thickness and the viscosity grades of HPMC. The cores containing antipyrine as the model drug was prepared by tabletting and retarding, and enteric coats were applied in a

fluidized bed coater. The system is suitable for both tablets and capsules [21].

TIME CLOCK' System

The Time Clock® system (West Pharmaceutical Services Drug Delivery & Clinical Research Centre) consists of a solid dosage form coated with lipidic barriers containing carnauba wax and bees' wax along with surfactants, such as span 80. After a lag time proportional to the thickness of the film, this coat erodes or emulsifies in the aqueous environment, and the core is then available for dispersion. A study with human volunteers has shown that the lag time was independent of gastric residence time, and the hydrophobic film redispersion did not appear to be influenced by mechanical action of stomach or gastrointestinal pH or the presence of intestinal enzymes [22]. The lag time increased with increasing coating thickness. Such systems are better suited for water-soluble drugs. Few problems associated with erosion-controlled systems include a premature drug release when the penetrating dissolution fluid dissolves the drug, which diffuses out through the barrier layers, and sustained release after the lag phase when the barrier layer is not eroded or dissolved completely, thereby retarding the drug release[23].

Compressed Tablets

These are timed release formulations, simple to manufacture, comprised of an inner core that contains an API and excipients surrounded by an outer layer that dissolves or disintegrates slowly to produce the lag time. The core is placed between two layers of polymer and directly compressed by flat punches of tabletting machine. Surrounding polymeric layers protect the drug from release before the desired lag time, hence effective delivery in chronotherapy as it allows the drug release at the point in circadian cycle when clinical signs develop and increase[24].

Multilayered Tablets

In this system a release pattern with two pulses was obtained from a three-layered tablet containing two drug containing layers separated by a drug-free gellable polymeric barrier layer[25]. This three-layered tablet was coated on three sides with impermeable ethyl cellulose, and the top portion was left uncoated. On contact with dissolution medium, the initial dose incorporated into the top layer was released rapidly from the non-coated surface. The second pulse was obtained from the bottom layer after the gelling barrier layer of HPMC was eroded and dissolved. The appearance of the second pulse was controlled by the rate of gelling and/or dissolution of the barrier layer. The gelling polymers reported include cellulose derivatives like HPMC, methyl cellulose, some classes of methacrylates (Eudragits®) or polyvinyl alcohols of various molecular weights and the coating materials include ethyl cellulose, cellulose acetate- propionate, methacrylic polymers, acrylic and mehtacrylic co-polymers, and polyalcohol's. A marketed

product of this class is *SyncroDose*™ [26].

B. Multi Unit Pulsatile System

Multi-particulate drug delivery systems are mainly oral dosage forms consisting of a multiplicity of small discrete units, in which the active substance is present as a number of small independent subunits. They provide many advantages over single-unit systems because of their small size, less inter and intra-subject variability in gastrointestinal transit time, reduced adverse effects and improved tolerability, no risk of dose dumping, flexibility in design and finally Improve stability. However, there are some draw backs in this system, which include lack of manufacturing reproducibility, high cost of production, multiple formulation steps and also the need of advanced technologies [27].

Pulsatile system based on rupturable coating

This is a multiparticulate system in which drug is coated on non-pareil sugar seeds followed by a swellable layer and an insoluble top layer. The swelling agents used include superdisintegrants like sodium carboxymethyl cellulose, sodium starch glycollate, L-hydroxypropyl cellulose, etc. Upon absorption of water, the swellable layer expands, resulting in rupture of film with subsequent rapid drug release. The lag time can be varied by varying coating thickness or adding high amounts of lipophilic plasticizer in the outermost layer [28]. In recent times different systems based on hard gelatin capsules and tablet core were illustrated, all coated by outer rupturable layer and inner swellable. The film rupture may be attained by swelling, osmotic or effervescent additives (citric acid &sodium bicarbonate) in the reservoir [29]. By optimizing the system, drug release can be obtained at specific time Interval.

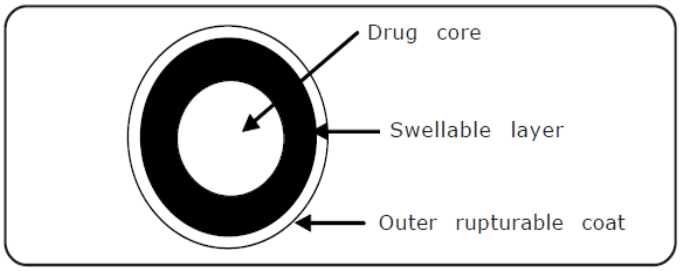

Figure 5: Schematic Diagram of Deliver Systems with Rupturable Coating Layer[54].

Osmotic based rupturable coating system

This system is based on a combination of osmotic and swelling effects. The core containing the drug, a low bulk density solid and/or liquid lipid material (eg, mineral oil) and a disintegrant was prepared. This core was 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 [30].

Pulsatile delivery by change in membrane permeability

These systems are designed when a sigmoidal release pattern is desired, therapeutically beneficial for timed release and colonic drug delivery. Drug release is achieved by change in permeability of polymeric coating layer in presence of certain counter ions of surrounding media. The release profile of systems based on permeability changes depend strongly on physicochemical properties of the drug and its interaction with membrane. Therefore, with this system a pulsatile release profile may be obtained for some particular drug molecules in a specific formulation but cannot be generally applied to all drugs [31].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 [32].This ion exchange has been used to develop several delivery systems. Eudragit RS 30D is reported to be a polymer of choice for this purpose. It typically contains positively polarized quaternary ammonium group in the polymer side chain, which is always accompanied by negative hydrochloride counter-ions. The ammonium group being hydrophilic 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[33].

II. Stimuli induced pulsatile systems:

In these systems there is release of the drug after stimulation by any biological factor like temperature, or any other chemical stimuli. These systems are further classified in to temperature induced systems and chemical stimuli induced system, on the basis of stimulus.

A. THERMO-RESPONSIVE PULSATILE RELEASE

Temperature induced systems

Thermo-responsive hydrogel systems have been developed for pulsatile release. In these systems the polymer undergoes swelling or deswelling phase in response to the temperature which modulate drug release in swollen state [34]. Kataoka et al developed the thermosensitive polymeric micelles as drug carrier to treat the cancer. They used end functionalized poly (*N*-isopropylacrylamide) (PIPAAm) to prepare corona of the micelle which showed hydration and dehydration behavior with changing temperature [35].

B. 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. 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 includes N,Ndimethylaminoethyl methacrylate, chitosan, polyol etc[36].These hydrogels showed a glucose-responsive, sol–gel phase transition dependent upon the external glucose concentration.

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. Yui and co-workers focused on the inflammatory induced

Hydroxyl radicals and designed drug delivery systems, which responded to the hydroxyl radicals and degraded in a limited manner. They used hyaluronic acid (HA) which is specifically degraded by the hyaluronidase or free radicals. Degradation of HA via the hyaluronidase is very low in a normal state of health. Degradation via hydroxyl radicals however, is usually dominant and rapid when HA 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 [37].

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 interactions are 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 [38].

pH sensitive drug delivery system

Such type of pulsatile drug delivery system contains two components one is of immediate release type and other one is pulsed release which releases the drug in response to change in pH. In case of pH dependent system advantage has been taken of the fact that there exists different pH environment at different parts of the gastrointestinal tract. By selecting the pH dependent

polymers drug release at specific location can be obtained. Examples of pH dependent polymers include cellulose acetate phthalate, polyacrylates, and sodium carboxymethylcellulose. These polymers are used as enteric coating materials so as to provide release of drug in the small intestine [39].

III. EXTERNAL STIMULI PULSATILE RELEASE

This system was divided into five subparts and is discussed below.

A. 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. Another development in MEMS technology is the microchip. The microchip consists of an array of reservoirs that extend through an electrolyte-impermeable substrate. The prototype microchip is made of silicon and contains a number of drug reservoirs; each reservoir is sealed at one end by a thin gold membrane of material that serves as an anode in an electrochemical reaction and dissolves when an electric potential is applied to it in an electrolyte solution. The reservoirs are filled with any combination of drug or drug mixtures in any form (i.e. solid, liquid or gel). When release is desired, an electric potential is applied between an anode membrane and a cathode, the gold membrane anode dissolves within 10-20 seconds and allows the drug in the reservoir to be released. This electric potential causes oxidation of the anode material to form a soluble complex with the electrolytes which then dissolves allowing release of the drug[40]. Complex release patterns (such as simultaneous constant and pulsatile release) can be achieved from the microchips. Microchip has the ability to control both release time and release rate.

B. 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[41].

C. Electro Responsive Pulsatile Release

Electrically responsive delivery systems are prepared from 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. Examples of naturally occurring polymers include hyaluronic acid, chondroitin sulphate, agarose, carbomer, xanthan gum and calcium alginate. The synthetic polymers are generally acrylate and methacrylate derivatives such as partially hydrolyzed polyacrylamide, polydimethylaminopropyl acryl amide [42].

D. Ultrasound induces release

Ultrasound is mostly used as an enhancer for the improvement of drug permeation through biological barriers, such as skin. The interaction of ultrasound with biological tissues is divided into two broad categories: thermal and nonthermal effects. Thermal effects are associated with the absorption of acoustic energy by the fluids or tissues [43]. Non-thermal bio-effects are generally associated with oscillating or cavitating bubbles, but also include noncavitation effects such as radiation pressure, radiation torque, and acoustic streaming.

E. Light induces release

Light-sensitive hydrogels have potential applications in developing optical switches, display units, and ophthalmic drug delivery devices. 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 LCST41, hydrogel collapses and result in an increased rate of release of soluble drug held within the matrix [44].

IV. Multiparticulate Systems

Multiparticualte systems (eg, 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 [45].

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[46]. Superdisintegrants like sodium carboxymethyl cellulose, sodium starch glycollate, 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. The

release is independent of environmental factors like pH and drug solubility. The lag time depends on coating thickness and amounts and type of plasticizer incorporated in the outermost layer. A rapid release after the lag phase was achieved with increased concentration of osmotic agent. *In-vivo* studies of time-controlled explosion system (TCES) with an *in-vitro* lag time of three hours showed appearance of drug in blood after 3 hours, and maximum blood levels after 5 hours [47].

Sigmoidal Release System:

This consists of pellet cores containing drug and succinic acid coated with ammonio-methacrylate copolymer USP/NF type B[48]. 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, malic acid, 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 corr. The *in-vitro* lag time correlated well with *in-vivo* data when tested in beagle dogs [49].

Low Density Floating Multiparticulate Pulsatile Systems:

Conventional multiparticulate pulsatile release dosage forms mentioned above are having longer residence time in the gastrointestinal tract and due to highly variable nature of gastric emptying process may result in in vivo variability and bioavailability problems. In contrary, low density floating multiparticulate pulsatile dosage forms reside only in stomach and not affected by variability of pH, local environment or gastric emptying rate. These dosage forms are also specifically advantageous for drugs either absorbed from the stomach or requiring local delivery in stomach[50].

V. 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 [51]. 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 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 [52].

Table 2. Marketed Technologies of Pulsatile Delivery[55].

Technology	Mechanism	Proprietary name and dosage form	API	Disease
OROS®	Osmotic mechanism	Covera-HS®; XL tablet	Verapamil HCl	Hypertension
Three dimensional printing	Externally regulated system	Their Form®	Diclofenac Sodium	Inflammation
DIFFUCAPS	Multiparticulate	Innopran®; XL tablets	Verapamil HCL, Propranolol HCL	Hypertension
Pulsincap™	Rupturable system	Pulsincap™	Dofetilide	Hypertension
CODAS®	Multiparticular pH dependent system	Verelan® PM; XL release capsule	Verapamil HCl	Hypertension

CONCLUSION

It is known that sustained and controlled release products provide a desired therapeutic effect, but fall for diseases following biological rhythms. So there is a constant need for new delivery systems that can provide increased therapeutic benefits to the patients by delivering drug at the right time, right place & in right amounts to coincide with circadian rhythm of body. Various methodologies are employed for developing pulsatile drug delivery like time controlled, stimuli induced, externally regulated system and multiparticulate drug delivery system. These considerations, along with the potential therapeutic benefits of pulsatile drug delivery systems, should ensure that the current high level of interest in this area would stretch well into future and ensures the betterment of quality life.

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