PULSATILE DRUG DELIVERY SYSTEM: A REVIEW
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ABSTRACT
Pulsatile drug delivery system is the most interesting time and site specific system. This system is designed for chronopharmacotherapy which is based on the circadian rhythm. The present study is aiming at the development of Chronotherapy is designed accordingly to the chronological behavior of body. Although oral delivery has become a widely accepted route of administration of therapeutic drugs, the gastrointestinal tract presents several formidable barriers to drug delivery. The increasing research interest surrounding ChrDDS (chronic drug delivery systems) may lead to the creation of a new discipline in pharmaceutics known as chronopharmaceutics. Such novel and more biological approaches may lead to safer and more efficient disease therapy in future. 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, Necessity of PDDS, methodologies involved for the existing systems, and PDDS product currently available in the market.

KEY WORDS
Chronotherapy, Chronopharmaceutics, Pulsatile Drug Delivery System (PDDS), chronological behavior.

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INTRODUCTION

Pulsatile systems are gaining a lot of interest as they deliver the drug at the right site of action at the right time and in the right amount, thus providing spatial and temporal delivery and increasing patient compliance. The release of the drug as a pulse after a lag time has to be designed in such a way that a complete and rapid drug release follows the lag time. These systems are designed according to the circadian rhythm of the body. 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[1].

Chronopharmacotherapy

Recent studies show that diseased have predictable cyclic rhythms and the timing of medication regimens can improve outcome in selected chronic conditions.

“Chronopharmaceutics” consist of two words chronobiology and Pharmaceutics. Chronobiology is the study of biological rhythms and their mechanisms.

There are three types of mechanical rhythms in our body, they are

- Circadian
- Ultradian
- Infradian

Circadian: “Circa” means about and “dies” means day

Ultradian: Oscillation of shorter duration are termed as ultradian (more than one cycle per 24 h)

Infradian: Oscillations that are longer than 24 h (less than one cycle per day) [2].

Necessity of Pulsatile Drug Delivery Systems

There are many conditions and diseases where sustained release formulations do not show good efficacy so these conditions demand the release of drug after a lag time in, in other words it is required that the drug should not release at all during the initial phase of dosage form administration. In such cases Pulsatile DDS is applicable.

1. Many body functions follow circadian rhythm, i.e., their activity increases or decreases with time. A number of hormones like rennin, aldosterone, and cortisol show daily as well as timely fluctuations in their blood levels. Circadian effects are also observed in case of pH and acid secretion in stomach, gastric emptying, and gastro-intestinal blood transfusion.

2. Severity of diseases like bronchial asthma, myocardial infarction, angina pectoris, rheumatic disease, ulcer, and hypertension is time dependent. Sharp increase in asthmatic attacks during early morning hours have been reported by Dethlefsan and Repges such a condition demands supplement of drug at particular time rather than maintaining constant plasma drug level. A drug delivery system administered at bedtime, but releasing drug as a burst after the time of administration (during morning hours), would be ideal in this case. Same is true for preventing heart attacks in the
middle of the night and the morning stiffness typical of people suffering from arthritis.

3. Drugs like Salbutamol sulphate produce biological tolerance and hence demand for a system that will prevent their continuous presence at the site of action as this tends to reduce their therapeutic effect.

4. Protection from gastric environment is essential for the drugs that undergo degradation in gastric acidic medium (e.g., peptide drugs), irritate the gastric mucosa (NSAIDS) or induce nausea and vomiting. These conditions can be satisfactorily handled by enteric coating, and in this sense, enteric coating can be considered as a pulsatile drug delivery system.

5. To achieve localized action at distal organs of GIT such as colon for drugs used in ulcerative colitis (e.g. Sulfasalazine) the drug release needs to be prevented in the upper two-third portion of the GIT.

6. The drugs that undergo extensive first-pass metabolism (β-blockers) and those that are characterized by idiosyncratic pharmacokinetics or pharmacodynamics resulting in reduced bioavailability, altered drug/metabolite ratios, altered steady state levels of drug and metabolite, and potential food-drug interactions require delayed release of the drug to the extent possible[3].

All of these conditions demand for an efficiently programmed drug delivery system releasing the right amount of drug at the right time. This can be achieved by Pulsatile Drug Delivery Systems. A pulsatile drug delivery system is characterized by a rapid drug release after a predetermined lag time that is an interval of no drug release.

**Fig 1: Drug release profile of pulsatile drug delivery systems**[4].

Marketed technologies of pulsatile delivery are shown in Table 1 and Drugs used according to chronological behavior 2[4].
Table 1. Marketed Technologies of Pulsatile Delivery.

| Technology   | Mechanism                        | Proprietary name and dosage form | API          | Disease       |
|--------------|----------------------------------|----------------------------------|--------------|---------------|
| OROS*        | Osmotic mechanism                | Covera-H5*; XL                   | Verapamil    | Hypertension  |
| Three        | Externally regulated system      | Their Form*                      | Diclofenac Sodium | Inflammation  |
| dimensional  |                                  |                                  |              |               |
| DIFFUCAPS*   | Multiparticulate                 | Innopran*; XL tablets            | Verapamil HCL, Propranolol HCL | Hypertension  |
| PulsincapTM  | Rupturable system                | PulsincapTM                      | Dofetilide   | Hypertension  |

Table 2. Drugs used According to Chronological Behavior.

| Chronological behavior                                      | Drugs used                               | Diseases              |
|-------------------------------------------------------------|------------------------------------------|-----------------------|
| Acid secretion is high in the Afternoon and at night        | H2 blockers                             | Peptic ulcer          |
| Precipitation of attacks during night or at early morning   | β2 agonist, Antihistamines              | Asthma                |
| BP is at its lowest during the sleep cycle and rises steeply during the early morning | Nitroglycerin, calcium channel blocker, ACE inhibitors | Cardiovascular diseases |
| Pain in the morning and more pain at night                  | NSAIDs, Glucocorticoids                 | Arthritis             |
| Increase in the blood sugar level after meal                | Sulfonylurea, Insulin                   | Diabetes mellitus     |
| Cholesterol synthesis is generally higher during night than day time | HMG CoA reductase inhibitors           | Hypercholesterolemia  |
Methodologies for PDDS

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

I. Time controlled pulsatile release
   A. Single unit system
   B. Multi-particulate system

II. Stimuli induced
   A. Thermo-Responsive Pulsatile release
   B. Chemical stimuli induced pulsatile systems

III. External stimuli pulsatile release
   A. Electro responsive pulsatile release
   B. Magnetically induced pulsatile release

IV. Pulsatile release systems for vaccine and hormone products

**TIME CONTROLLED PULSATILE RELEASE SYSTEM**

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

**Single Unit Systems**

**Delivery by Solubility Modulation**

These systems contain a solubility modulator for pulsed delivery of variety of drugs. The system was especially developed for delivery of salbutamol sulphate \(^{[5]}\). The compositions contain the drug (salbutamol sulphate) and a modulating agent, sodium chloride (NaCl). The amount of NaCl was such that it was less than the amount needed to maintain saturation in a fluid that enters the osmotic device. The pulsed delivery is based on drug solubility. Salbutamol has solubility of 275 mg/ml in water and 16 mg/ml in saturated solution of NaCl, while NaCl has solubility of 321 mg/ml in water, and its saturation solubility is 320 mg/ml. These values show that the solubility of the drug is a function of the modulator concentration, while the modulators solubility is largely independent of drug concentration. The modulating agent can be a solid organic acid, inorganic salt or organic salt.

**Port Systems**

The Port System - consists of a gelatin capsule coated with a semi permeable membrane (e.g: cellulose acetate) housing an insoluble plug (e.g: lipidic) and an osmotically active agent along with the drug formulation\(^{[6]}\). When it comes in contact with the aqueous medium, water diffuses across the semi permeable membrane, resulting in increased inner pressure that ejects the plug after a – time lag. The time lag is controlled by the thickness of semi
permeable membrane. The system showed good correlation in lag times of in-vitro and in-vivo experiments in humans[7]. In order to deliver drug in liquid form, an osmotically driven capsular system was developed. In this system, liquid drug is absorbed into highly porous particles, which release the drug through an orifice of a semi permeable capsule supported by an expanding osmotic layer after the barrier layer is dissolved[8]. The capsular system delivers drug by the capsule's osmotic infusion of moisture from the body. The capsule wall is made up of an elastic material and possesses an orifice. As the osmosis proceeds, the pressure within the capsule rises, causing the wall to stretch. The orifice is small enough so that when the elastic wall relaxes, the flow of the drug through the orifice essentially stops, but when the elastic wall is distended beyond threshold value, the orifice expands sufficiently to allow drug release at a required rate. Elastomers, such as styrene-butadiene copolymer have been suggested[9, 10].

**Capsular Systems**

Different single-unit capsular PDDS have been developed. A general design of such systems consists of an insoluble capsule body housing a drug and a plug. The plug is removed after a predetermined time lag due to swelling, erosion, or dissolution. The Pulsincap® system is an example of such a system that is made up of a water-insoluble capsule body filled with drug formulation[11]. The body is closed at the open end with a swellable hydrogel plug. Upon contact with dissolution medium or gastro-intestinal fluids, the plug swells, pushing itself out of the capsule after a time lag. This is followed by a spontaneous release of the drug. The time lag can be controlled by manipulating the dimension and the position of the plug. For water insoluble drugs, a spontaneous release can be ensured by inclusion of effervescent agents or disintegrants. The plug material consists of insoluble but permeable and swellable polymers e.g.: polymethacrylates) [12, 13], erodible compressed polymers (e.g: hydroxypropylmethyl cellulose, polyvinyl alcohol, polyethylene oxide), congealed melted polymers (e.g: saturated polyglycolated glycerides, glycerylmonoole and enzymatically controlled erodible polymer e.g:pectin). These formulations are well tolerated in animals and healthy volunteers, and there have been no reports of gastro-intestinal irritation. However, there was a potential problem of variable gastric residence time, which was overcome by enteric coating the system to allow its dissolution only in the higher pH region of small intestine.
Delivery by a Series of Stops

This system is described for implantable capsules. The capsule contains a drug and a water-absorptive osmotic engine that are placed in compartments separated by a movable partition. The pulsatile delivery is achieved by a series of stops along the inner wall of the capsule. These stops obstruct the movement of the partition but are overcome in succession as the osmotic pressure rises above a threshold level. The number of stops and the longitudinal placements of the stops along the length of the capsule dictate the number and frequency of the pulses, and the configuration of the partition controls the pulse intensity. This system was used to deliver porcine somatotropin.[14]

Delivery by Reservoir Systems with Erodible or Soluble Barrier Coatings

Most of the pulsatile drug delivery systems are reservoir devices coated with a barrier layer. This barrier erodes or dissolves after a specific lag period, and the drug is subsequently released rapidly. The time lag depends on the thickness of the coating layer.[15] The Time Clock® system consists of a solid dosage form coated with lipid barriers containing carnauba wax and bees wax along with surfactants, such as polyoxyethylene sorbitan monooleate.[16, 17] This coat erodes or emulsifies in the aqueous environment in a time proportional to the thickness of the film, and the core is then available for dispersion. The major advantage of this system is its ease of manufacture without any need of special equipment. The disadvantage of this system is a premature drug release when the penetrating water dissolves the drug. The Chronotropic® system consists of a drug-containing core coated by hydrophilic swellable hydroxypropylmethyl cellulose (HPMC), which is responsible for a lag phase in the onset of drug release.[18] Time lag is controlled by the thickness and the viscosity grades of HPMC used in coating the drug core. The system is suitable for both tablets and capsule formulations.[19]

Multiparticulate Systems:

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

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

Pulsatile Delivery by Change in Membrane Permeability

The permeability and water uptake of acrylic polymers with quaternary ammonium groups can be influenced by the presence of different counter-ions in the medium.[20] Several delivery systems based on this ion exchange have been developed. Eudragit RS 30D is reported to be a polymer of choice for this purpose.[21] It typically contains positively polarized quaternary ammonium group in the polymer side chain, which is always accompanied by negative hydrochloride counter-ions. The ammonium group being
hydrophilic it facilitates the interaction of polymer with water, thereby changing its permeability and allowing water to permeate the active core in a controlled manner.

**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\(^{[22]}\).

**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\(^{[23, 24]}\). The swelling agents used include superdisintegrants like sodium carboxymethyl cellulose, sodium starch glycollate, L-hydroxypropyl cellulose, etc. Upon ingress of water, the swellable layer expands, resulting in rupture of film with subsequent rapid drug release. The release is independent of environmental factors like pH and drug solubility. The lag time can be varied by varying coating thickness or adding high amounts of lipophilic plasticizer in the outermost layer.

**Time Controlled Expulsion System**

This system is based on a combination of osmotic and swelling effects. The core contains the drug, a low bulk density solid and/or liquid lipid material (e.g., mineral oil) and a disintegrant. The core is further coated with cellulose acetate. Upon immersion in aqueous medium, water penetrates the core displacing the lipid material. After the depletion of lipid material, internal pressure increases until a critical stress is reached, which results in rupture of the coating material\(^{[25]}\). Another system is based on a capsule or tablet composed of a large number of pellets consisting of two or more pellets or part\(^{[26]}\).

**Sigmoidal Release System**

This consists of pellet cores comprising drug and succinic acid coated with ammonio-methacrylate copolymer USP/NF type B. The time lag is controlled by the rate of water influx through the polymer membrane. The water dissolves acid and the drug in the core. The acid solution in turn increases permeability of the hydrated polymer film. The different types of acids that can be used include succinic acid, acetic acid, glutaric acid, tartaric acid, malic acid, or citric acid\(^{[27,28]}\).

**STIMULI INDUCED PULSATILE RELEASE SYSTEM**

Several polymeric delivery systems undergo phase transitions and demonstrate marked swelling-deswelling changes in response to environmental changes including solvent composition, ionic strength, temperature, electric fields, and light\(^{[29]}\). Responsive drug release from those systems results from the stimuli-induced changes in the gels or in the micelles, which may deswell, swell, or erode in response to the respective stimuli. The mechanisms of drug release include ejection of the drug from the gel as the fluid phase synerges out, drug diffusion along a concentration gradient, electrophoresis of charged drugs towards an
oppositely charged electrode and liberation of the entrapped drug as the gel or micelle complex erodes\textsuperscript{30}.

**Chemical Stimuli Induced Pulsatile Systems**

**Inflammation-stimulated Pulsatile Release**

On receiving any physical or chemical stress, such as injury, fracture etc., inflammation take place at the injured sites. During inflammation, hydroxyl radicals are produced from these inflammation-responsive cells. Degradation via hydroxyl radicals however, is usually dominant and rapid when Hyaluronic Acid gel is injected at inflammatory sites. Thus, it is possible to treat patients with inflammatory diseases like rheumatoid arthritis; using anti-inflammatory drug incorporated HA gels as new implantable drug delivery systems\textsuperscript{31}.

**pH Sensitive Drug Delivery System**

This type of PDDS contains two components. The first is fast release type while the other is pulsed release which releases the drug in response to change in pH. In case of pH dependent system, advantage has been taken of the fact that there exists different pH environment at different parts of the gastrointestinal tract. By selecting the pH dependent polymers drug release at specific location can be obtained. Examples of pH dependent polymers include cellulose acetate phthalate, polyacrylates, and sodium carboxymethylcellulose. These polymers are used as enteric coating materials so as to provide release of drug in the small intestine\textsuperscript{32}.

**Glucose-responsive Insulin Release Devices**

In case of Diabetes mellitus there is rhythmic increase in the levels of glucose in the body, requiring injection of the insulin at proper time. Several systems have been developed which are able to respond to changes in glucose concentration. One such system includes pH sensitive hydrogel containing glucose oxidase immobilized in the hydrogel. When glucose concentration in the blood increases glucose oxidase converts glucose into gluconic acid which changes the pH of the system. This pH change induces swelling of the polymer which results in insulin release. Insulin by virtue of its action reduces blood glucose level and consequently gluconic acid level also gets decreased and system turns to the deswelling mode thereby decreasing the insulin release. Examples of the pH sensitive polymers include N, N-dimethylaminoethyl methacrylate, chitosan, polyol etc.\textsuperscript{33, 34}.

**EXTERNAL STIMULI PULSATILE RELEASE**

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

**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\textsuperscript{35, 36}. The digital capabilities of MEMS may allow greater temporal control over drug release compared to traditional polymer-based systems. Another development in MEMS technology is the microchip. The microchip consists of an array of reservoirs that extend through an electrolyte-impermeable substrate. The prototype microchip is made of silicon and contains a number of drug reservoirs; each reservoir is sealed at one end by a thin gold membrane of material that serves as an anode in an electrochemical reaction and dissolves when an electric potential is applied to it in an
electrolyte solution. The reservoirs are filled with any combination of drug or drug mixtures in any form (i.e. solid, liquid or gel). When release is desired, an electric potential is applied between an anode membrane and a cathode, the gold membrane anode dissolves within 10-20 seconds and allows the drug in the reservoir to be released. This electric potential causes oxidation of the anode material to form a soluble complex with the electrolytes which then dissolves allowing release of the drug. Complex release patterns (such as simultaneous constant and pulsatile release) can be achieved from the microchips. Microchip has the ability to control both release time and release rate.

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[37].

Electro Responsive Pulsatile Release

Electrically responsive delivery systems are prepared from polyelectrolytes (polymers which contain relatively high concentration of ionisable groups along the backbone chain) and are thus, pH responsive as well as electro-responsive. Examples of naturally occurring polymers include hyaluronic acid, chondroitin sulphate, agarose, carbomer, xanthan gum and calcium alginate. The synthetic polymers are generally acrylate and methacrylate derivatives such as partially hydrolyzed polyacrylamide, polydimethylaminopropyl acrylamide[35].

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[38]. 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[39]. 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.

CONCLUSION

Research in chronopharmacology has demonstrated the importance of biological rhythms in drug therapy and this has led to a new approach to the development of drug delivery systems. Optimal clinical outcome cannot be achieved if drug plasma concentrations are constant. Circadian disorders such as hypertension, osteoarthritis, Asthma etc., which require chronopharmacotherapy. PDDS can effectively tackle this problem as it is modulated according to body's circadian clock giving release of drug after a specified time lag. Pulsatile release systems should be promising in the future.
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