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The Latest Methods and Technologies of Pulsatile Drug Delivery System: A Review

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Abstract

Pulsatile drug delivery systems (PDDS) have multiple benefits over conventional dosage forms , drugs are released in an immediate or extended manner. A pulsatile drug release, where the drug is released rapidly after a well defined lag-time, could be advantageous for many drugs or therapies. They deliver the drug at the right time, at the right site of action and in the right amount, which provides more benefit than conventional dosages and increased patient compliance. These systems are designed according to the circadian rhythm of the body and the drug is released as a pulse. Diseases like asthma, peptic ulcers, cardiovascular ailments, arthritis and attention deficit syndrome in children and hypercholesterolemia can be cured by drugs, released by PDDS. This review covers methods and marketed technologies that have been developed to achieve pulsatile delivery. Marketed technologies, such as Pulsincap™, Diffucaps®, CODAS®, OROS® and PULSYS™, follow the above mechanism to render a sigmoidal drug release profile. Diseases wherein PDDS are promising include asthma, peptic ulcers, cardiovascular ailments, arthritis and attention deficit syndrome in children and hypercholesterolemia. Pulsatile drug delivery systems have the potential to bring new dents in the therapy of many diseases.

Key words: Pulsatile, Chronotherepy, Lag-time.

Introduction

Oral controlled drug delivery systems represent the most popular form of controlled drug delivery systems for the obvious advantages of oral route of drug administration. Such systems release the drug with constant or variable release rates[4]. These dosage forms offer many advantages, such as nearly constant drug level at the site of action, prevention of peak-valley fluctuations, reduction in dose of drug, reduced dosage frequency, avoidance of side effects, and improved patient compliance. [5,7]

However, there are certain conditions for which such a release pattern is not suitable. These conditions demand release of drug after a lag time. In other words, it is required that the drug should not be released at all during the initial phase of dosage form administration.[2] Such a release pattern is known as pulsatile release's pulsatile drug delivery system is characterized by a lag time that is an interval of no drug release followed by rapid drug release.[10]

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.[5]

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In chronopharmacotherapy drug administration is synchronized with biological rhythms to produce maximal therapeutic effect & minimum harm for the patient. Technically, pulsatile drug delivery systems administered via the oral route could be divided into two distinct types, the time controlled delivery systems and the site-specific delivery systems, thus providing special and temporal delivery. In recent Pharmaceutical applications involving pulsatile delivery; multiparticulate dosage forms (e.g. pellets) are gaining much favor over single-unit dosage forms. Designing of proper pulsatile drug delivery will enhance the patient compliance, optimum drug delivery to the target side & minimizing the undesired effects.[9]

The shift from conventional sustained release approach to modern pulsatile delivery of drugs can be credited to the following reason(s):[4,7,9,12]

1. **First pass metabolism**

Some drugs, such as beta blockers, and salicylamide, undergo extensive first pass metabolism and require fast drug input to saturate metabolizing enzymes in order to minimize pre-systemic metabolism. Thus, a constant/sustained oral method of delivery would result in reduced oral bioavailability.

2. **Biological tolerance**
Continuous release drug plasma profiles are accompanied by a decline in the pharmacotherapeutic effect of the drug, e.g. biological tolerance of transdermal nitroglycerin.

3. **Special chronopharmacological needs**
Circadian rhythms in certain physiological functions are well established. It has been recognized that many symptoms and onset of disease occur during specific time period of the 24 hour day, e.g., asthma and angina pectoris attacks are most frequently in the morning hours.

4. **Local therapeutic need**
For the treatment of local disorders such as inflammatory bowel disease, the delivery of compounds to the site of inflammation with no loss due to absorption in the small intestine is highly desirable to achieve the therapeutic effect and to minimize side effects.

5. **Gastric irritation or drug instability in gastric fluid**
For compounds with gastric irritation or chemical instability in gastric fluid, the use of a sustained release preparation may exacerbate gastric irritation and chemical instability in gastric fluid.

6. **Drug absorption differences in various gastrointestinal segments**
In general, drug absorption is moderately slow in the stomach, rapid in the small intestine, and sharply declining in the large intestine. Compensation for changing absorption characteristics in the gastrointestinal tract may be important for some drugs. For example, it is rational for a delivery system to pump out the drug much faster when the system reaches the distal segment of the intestine, to avoid the entombment of the drug in the feaces.

Ideal pulsatile drug delivery system [12]
Pulsatile drug delivery system is defined as the rapid and transient release of certain amount of drug molecules within a short time period immediately after a predetermined off-release period, i.e., lag time. Pulsatile drug delivery aims to release drug on programmed pattern i.e. appropriate time and at appropriate site of action.
A single dosage form provides initial dose of drug followed by one release free interval, after which second dose of drug is released, which is followed by additional release-free interval and pulse of drug release.

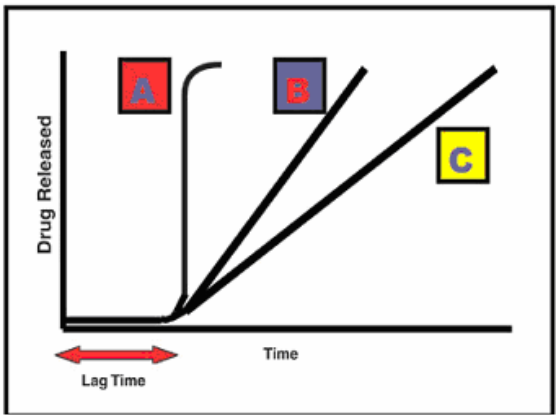

Figure No. 1: Drug release profile of pulsatile drug delivery system[2]
A: Ideal sigmoidal release B & C: Delayed release after initial lag time
The first pulsed delivery formulation that released the active substance at a precisely defined time point was developed in the early 1990s. In this context, the aim of the research was to achieve a so-called sigmoidal release pattern (pattern A in Figure1). The characteristic feature of the formulation was a defined lag time followed by a drug pulse with the enclosed active quantity being released at once.[9] Thus, the major challenge in the development of pulsatile drug delivery system is to achieve a rapid drug release after the lag time. Often, the drug is released over an extended period of time (patterns B & C in Figure1).
Nocturnal asthma, a condition prevalent in two-thirds of the asthmatics, is defined as a variable night time exacerbation of the underlying asthma condition associated with increase in symptoms and need for medication, increased airway responsiveness and worsening of lung function.Symptoms typically occur between midnight and 8 am, especially around 4.00 am. It is inconvenient to take the medication at midnight. The maintenance of constant drug level is not always desirable for the optimal therapy. A drug should be delivered only when and/or where it is needed at the minimum required dose4. For the drugs to follow circadian rhythm, like in asthma, a reasonable and an acceptable rationale is a delivery system capable of releasing drugs in a pulsatile fashion rather than as a continuous delivery at predetermined time/site following oral administration.[3,7]

Advantages of pulsatile drug release.[1,4]

- Extended daytime or night time activity.
- Reduced side effects
- Dosage frequency.
- Reduction in dose size.
- Improved patient compliance.
- Lower daily cost to patient due to fever dosage units are required by the patient .
- Drug adapts to suit circadian rhythms of body functions or diseases.
- Drug targeting to specific sites like colon.
- Protection of mucosa from irritating drugs.
- Drug loss is prevented by extensive first pass metabolism.

Drawbacks of Pulsatile Delivery:[3]

- Lack of manufacturing reproducibility and efficacy.
- Large number of process variables.
- Multiple formulation steps.
- Higher cost of production.
- Need of advanced technology.

Need of Pulsatile drug delivery System [8]

- Body function that follow circadian rhythms.
- When circadian rhythm is altered by the hormone such as rennin, aldosterone and cortisol etc level in blood.
- When rhythmic variation seen in acid secretion in stomach, gastric emptying, and gastrointestinal blood transfusion.
- Disease like bronchial asthma, myocardial infraction, angina pectoris, rheumatic disease, ulcer, and hypertension display time dependence.
- The lag time is essential for the drugs that undergo degradation in gastric acidic medium.
- It is possible to deliver the drugs to the distal part of GIT like colon targeting with pulsatile drug delivery.
- Drugs that undergo extensive first-pass metabolism are administered successfully as pulsatile drug delivery systems.

Diseases requiring pulsatile drug delivery [21]

Circadian rhythm regulates many body functions in humans, viz., metabolism, behaviour, Physiology, sleep patterns, hormone production, etc. Asthma is one such disease where pulsatile drug delivery system can be useful. Circadian changes are seen in normal lung function, which reaches a low point in the early morning hours. . In peptic ulcer acid secretion is high in the afternoon and at night. In case of cardiovascular diseases, BP is at its lowest during the sleep cycle and rises steeply during the early morning period. Platelet agreeability is increased and fibrinolytic activity is decreased in the morning, leading to a state of relative hypercoagulability of the blood. Circadian increase in the blood sugar level after meal has been observed in Diabetes mellitus. Circadian variations seen in DOPA level in afternoon in case of Attention deficit syndrome[7, 9, 10, 11].

Mechanism of drug release from pulsatile drug delivery system

The mechanism of drug release from PDDS can be occurring in the following ways[12]:

Diffusion

Water diffuses into the interior of the particle when particle come in contact with aqueous fluids in the gastrointestinal tract and resultant drug solutions diffuse across the release coat to the exterior.

Erosion

Some coatings designed to erode gradually with time, result in the release of drug contained within the particle.

Osmosis

An osmotic pressure can be built up within the interior of the particle when water allows entering under the right circumstances. The drug is forced out of the particle into the exterior through the coating.

"Chronopharmaceutics" consists 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.[5]

i. **Circadian:**" Circa" means about and "dies" means day.
ii. **Ultradian:**Oscillation of shorter duration are termed as ultradian (more than one cycle per 24 h)
iii. **Infradian:** Oscillations that are longer than 24 h (less than one cycle per day).

Chronobiology and Chronopharmacotherapy of Disease[27,28]

Chronotherapy is co-ordination of biological rhythms and medical treatment. Chronotherapeutic is the discipline concerned with the delivery of drugs according to inherent activities of a disease over a certain period of time. It is becoming increasingly more evident that the specific time that patients take their medication may be even more significant than was recognized in the past. The tradition of prescribing medication at evenly spaced time intervals throughout the day, in an attempt to

maintain constant drug levels throughout a 24-hour period, may be changing as researcher's report that some medications may work better if their administration is coordinated with day night patterns.

Table No. 1: Circadian rhythm and the manifestation of clinical diseases[17,20]

S.No.	Disease or syndrome	Circadian rhythmicity
1.	Allergic Rhinitis	Worse in the morning/upon rising
2.	Intraocular Pressure (IOP)	In glaucoma patients IOP peaks at 4 AM and has a trough in the afternoon, opposite that of people with normal IOP
3.	Asthma	Exacerbation more common during the sleep period
4.	Hormone Secretion	Growth hormone and melatonin are produced at night; testosterone and cortisol in the early morning hours
5.	Blood Coagulation	Even with constant heparin infusion rate, thromboplastin time and risk of bleeding vary significantly during the day
6.	Sudden cardiac death	Incidence higher in the morning after awakening
7.	Stroke	Incidence higher in the morning
8.	Myocardial Infraction	Incidence higher in the early morning
9.	Angina Pectoris	Chest pain and ECG changes more common in early morning
10	Osteoarthritis	Symptoms worse in the middle/later portion of the day
11	Rheumatoid Arthritis	Symptoms are most intense upon awakening

Many of circadian dependent diseases display symptoms in early morning hours or in the morning at awakening. It is well known that patients with asthma experience symptoms at night. Dyspnoea and peak of expiratory flow (PEF) values have been found to become worse during the night[4,24].

In chronopharmacotherapy (timed drug therapy) drug administration is synchronized with biological rhythms to produce maximal therapeutic effect and minimum harm for the patient. If symptoms occur at daytime a conventional dosage form can be administered just prior the symptoms are worsening. If symptoms of a disease became worse during the night or in the early morning the timing of drug administration and nature of the drug delivery system need careful consideration.

Control release systems for 12 or 24 hr drug release are not suitable for diseases, which follow circadian variation. In that condition there is requirement for time or pulsatile drug delivery system.

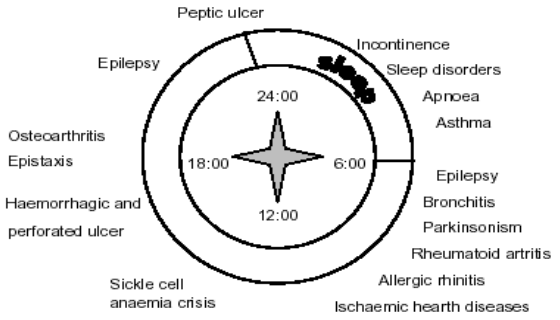

Figure No. 2: 24-hr clock diagram of the peak time of selected human circadian rhythm with reference to the day-night cycle.

Classification of Pulsatile Drug Delivery Systems:

Pulsatile drug delivery systems (PDDS) can be classified in site-specific and time-controlled systems. Drug release from site-specific systems depends on the environment in the gastro intestinal track, e.g., on pH, presence of enzymes, and the pressure in the gastro intestinal track. In contrast, time-controlled DDS are independent of the biological environment.[13]

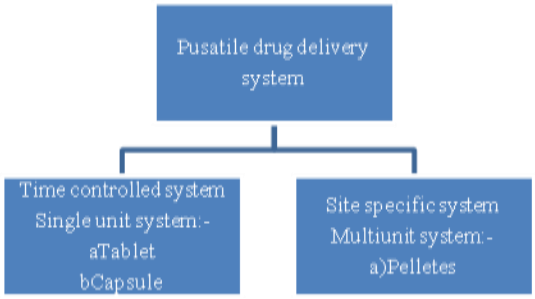

Figure No3: Classification of pulsatile drug delivery systems[3]

Methods of Development of Pulsatile Drug Delivery System

Different approaches of pulsatile system are:

1. Time Controlled system
    1. Pulsatile Delivery by Solubilisation or Erosion of layer
    2. Pulsatile Delivery by Rupture of Membrane
    3. Capsule Shaped Pulsatile Drug Delivery System
    4. Pulsatile System Based On Osmosis
2. Internally stimuli induced system

1.Temperature–induced pulsatile release

a) Thermo responsive hydro gel systems

b)Thermo responsive polymeric micelle systems

2. Chemical stimuli induced pulsatile release

a) Glucose-responsive insulin release devices

b)PH sensitive drug delivery system

c)Inflammation-induced pulsatile release

d)Drug release from intelligent gels responding

3. Externally Regulated System

a) Magnetic induces release

b) Ultrasound induces release

c) Electric field induces release

d) Light induces release

MULTIPARTICULATE SYSTEM

1.Time Controlled system

1.Pulsatile Delivery by Erosion of layer

In such systems the drug release is controlled by the dissolution or erosion of the outer coat which is applied on the core containing drug (Figure.3). The release of the active ingredient can be controlled by thickness and viscosity of the outer coat. The Time Clock system consists of a solid dosage form coated with lipid barriers containing carnauba wax and bees wax along with surfactants.

Chronotropic system consists of a core containing drug reservoir coated by a hydrophilic polymer HPMC.System is composed of a drug-containing core and swells able polymeric coating of HPMC which slow the interaction with aqueous fluids[4,8,9,11,13-17].

2. Pulsatile Delivery by Rupture of Membrane

These systems consist of an outer release controlling water insoluble but permeable coating subject to mechanically induced rupture phenomenon. The rupturing effect is achieved by coating the individual units with effervescent or swelling agents (Figure.4). Water permeation and mechanical resistance of the outer membrane are major factors affecting the lag time.

The lag time can be varied by varying coating thickness or adding high amounts of lipophilic plasticizer in the outermost layer [4, 8, 9,11,13-17].

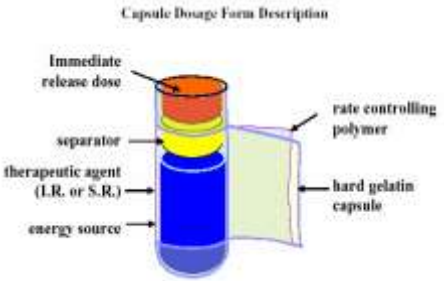

Figure No. 4: Single Unit PORT System [6,8]

3.Capsule Shaped Pulsatile Drug Delivery System

This dosage form consists of an insoluble capsule body containing drug and a release controlling plug (Soluble) is fitted between immediate release compartment and pulsed release compartment (Figure.5). The length of plug decides lag time. When it comes in contact with aqueous fluids, the cap rapidly dissolves thereby releasing the immediate release component followed by pulsed release component. Here the plug decides lag time which is inserted in to the body. A hydrostatic pressure generate inside the capsule that is why pulsatile drug delivery achieved[4, 8, 9,11,13-17].

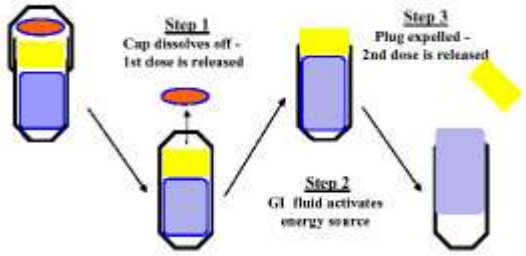

Figure No. 5: Drug release mechanism from PORT system [9]

4.Pulsatile System Based On Osmosis:

In this System, a capsule coated with semi permeable membrane is employed . There is an insoluble plug consisting of osmotically active agent and the drug formulation inside the capsule. This system divides the capsule interior into two compartments- one for the beneficial agent and the other for the osmotically active agent. Water diffuses across the semi permeable membrane when this cap comes into contact with GI fluids and it results in increased pressure inside that ejects the plug after a

predetermined lag time. Thickness of the coating decides the lag time. E.g. Ritalin (methyl phenidate) used in the treatment of attention deficit hyper active disorder (ADHD) in children[4,8,9,11,13-17.]

Tablets system:

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 lag time depends on the thickness of the coating layer. The Time ClockR system consists of a solid dosage form coated with lipidic barriers containing carnauba wax and bees wax along with surfactants, such as polyoxyethylene sorbitan monopaleate. 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. In a study with human Volunteers, it was shown that the lag time was independent of gastric residence time, and the hydrophobic film redispersion did not appear to be influenced by the presence of intestinal enzymes or mechanical action of stomach or gastro-intestinal pH. The lag time increased with increasing coating thickness. Such systems are better suited for water-soluble drugs. [2,34,37]

The major advantage of this system is its ease of manufacturing without any need of special equipment. However, such lipid-based systems may have high in-vivo variability (e.g., food effects). The possible problems of erosion-controlled systems include a premature drug release when the penetrating water 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.[16,20]

The **Chronotropic**R 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 release (10). In addition, through the application of an outer gastric-resistant enteric film, the variability in gastric emptying time can be overcome, and a colon-specific release can be obtained, relying on the relative reproducibility of small intestinal transit time. The lag time is controlled by the thickness and the viscosity grades of HPMC. The cores containing Antipyrine as the model drug were prepared by tabulating and retarding, and enteric coats were applied in a fluidized bed coater. The in-vitro release curves displayed a lag phase preceding drug release, and the in-vivo pharmacokinetic data showed a lag time prior to presence of detectable amounts of drug in saliva. Both in-vitro and in-vivo lag times correlate well with the applied amount of the hydrophilic retarding polymer. The system is suitable for both tablets and capsules.[1,15,22,34]

Multiparticulate systems:Multiparticualte systems (e.g., pellets) offer various advantages over single unit systems. These include no risk of dose dumping, flexibility of blending units with different release patterns, and 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 invariably a reservoir type with either rupturable or altered permeability coating.[19]

Pulsatile system based on rupturable coating:

Time-Controlled Explosion System (Fujisawa Pharmaceutical Co., Ltd.): 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 super disintegrants like sodium carboxymethyl cellulose, sodium starch glycollate, L-hydroxypropyl cellulose, polymers like polyvinyl acetate, polyacrylic acid, polyethylene glycol, etc. Alternatively, an effervescent system comprising a mixture of tartaric acid and sodium bicarbonate may also be used. 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. Varying coating thickness or adding high amounts of lipophilic plasticizer in the outermost layer can vary the lag time. 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 hr showed appearance of drug in blood after 3 hr, and maximum blood levels after 5 hr.[26,32]

Osmotic-based rupturable coating systems:

Permeability Controlled 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 (e.g., mineral oil) and a disintegrants were 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.

Another system is based on a capsule or tablet composed of a large number of pellets consisting of two or more pellets or parts (i.e., populations).

Each pellet has a core that contains the therapeutic drug and a water-soluble osmotic agent. Waterpermeable, water-insoluble polymer film encloses each core. A hydrophobic, water insoluble agent that alters permeability (e.g., a fatty acid, wax, or a salt of fatty acid) is incorporated into the polymer film. The rate of water influx and drug efflux causes the film coating of each population to differ from any other pellet coating in the dosage form. The osmotic agents dissolve in the water causing the pellets to swell, thereby regulating the rate of drug diffusion. The effect of each pellet population releasing its drug content sequentially provides a series of pulses of drug from a single dosage form. The coating thickness can be varied amongst the pellets. This system was used for the delivery of antihypertensive drug, diltiazem. Schultz and Kleinebudde reported the use of osmotically active agents that do not undergo swelling.

The pellet cores consisted of drug and sodium chloride. These were coated with a semi permeable cellulose acetate polymer. This polymer is selectively permeable to water and is impermeable to the drug. The lag time increased with increase in the coating thickness and with higher amounts of talc or lipophilic plasticizer in the coating. The sodium chloride facilitated the desired fast release of drug. In absence of sodium chloride, a sustained release was obtained after the lag time due to a lower degree of core swelling that resulted in generation of small fissures.

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. 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. 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, thereby changing its permeability and allowing water to permeate the active core in a controlled manner. This property is essential to achieve a precisely defined lag time.

The cores were prepared using theophylline as model drug and sodium acetate. These pellets were coated using Eudragit RS 30D (10% to 40% weight gain) in four different layer thicknesses. A correlation between film thickness and lag time was observed. It was found that even a small amount of sodium acetate in the pellet core had a dramatic effect on the drug permeability of the Eudragit film. After the lag time, interaction between the acetate and polymer increases the permeability of the coating so significantly that the entire active dose is liberated within a few minutes. The lag time increases with increasing thickness of the coat, but the release of the drug was found to be independent of this thickness.

1. Temperature–induced pulsatile release:

Temperature is the most widely applied triggering signal for a variety of triggered or pulsatile drug delivery systems. The body temperature often deviates from the physiological temperature (370 C) in the presence of pathogens or pyrogens. This deviation from normal range acts as a stimulus that triggers the release of therapeutic agents from several temperature-responsive drug delivery systems. Various polymer properties, including the thermally reversible coil/globule transition of polymer molecules, swelling change of networks, glass transition and crystalline melting utilized by temperature induced triggered drug delivery systems[3, 4, 10].

a)Thermo responsive hydro gel systems:

Hydro gels that undergo reversible volume changes in response to changes in temperature are known as thermo sensitive gels. In thermo-responsive hydro gel systems, hydro gels 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. As it undergo volume change, this property can be utilised to obtain a squeezing hydro gel device by positioning hydro gel within a rigid capsule. The reversible volume change of temperature-sensitive hydro gels accomplish onoff release e.g. PIPAAm cross-linked gels (Figure. 7) showed thermo responsive, off-and-on swelling/deswelling phases and it swells below 320 C temperature, on the other side shrink above this temperature[3,4,10].

b) Thermo responsive polymeric micelle systems**:**

Block copolymers were prepared by development of end functionalized PIPAA with hydrophobic polymers, such as poly (butyl methacrylate) (PBMA), polystyrene (PST) etc. In aqueous solution, block copolymers formed micellar structure (with core shell structure) below PIPAAm's transition temperature. In this system, drug is released when polymer undergoes swelling or deswelling phase in response to chemical reaction with membrane, alteration of pH and Inflammation induce3, 4, 10.

The shell was constructed from thermo responsive PIPAAm, while the core comprised of hydrophobic polymer aggregates. The PIPAAm corona exhibited a change in its hydration/dehydration properties with changing temperature.

2. Chemical stimuli induced pulsatile release:

a) Glucose-responsive insulin release devices:

These devices have been developed to respond with changes in glucose concentration in the blood. The hydro gels showed a glucose-responsive, sol–gel phase transition dependent upon the external glucose concentration. These devices also have pH sensitive hydro gel containing glucose oxidase immobilized in the hydro gel. When glucose concentration in the blood increases glucose oxidase converts glucose into gluconic acid which changes the pH of the system. This swelling of the polymer induced by this pH change 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[3, 7, 15, 16].

b) PH sensitive drug delivery system:

This system contains two components- one is of immediate release type and second is pulsed release which releases the drug in response to change in pH. As different pH environment exist at different parts of the gastrointestinal tract so this advantage is utilised by pH dependent system. By selecting the appropriate pH dependent polymers, desired drug release can be achieved at specific location. Examples of pH dependent polymers are 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[3, 7, 15, 16].

c) Inflammation-induced pulsatile release:

Any physical or chemical stress, such as injury, fracture etc. cause inflammation at the injured sites. The inflamed responsive cells produce hydroxyl radicals .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[5, 7,10,11,13].

d)Drug release from intelligent gels responding to antibody concentration

In the human body numerous kinds of bioactive compounds are exist. The change in concentration of these bioactive compounds can be detected by recently developed novel gels to alter their swelling/deswelling characteristics. Antigen antibody complex formation is of great importance as the cross-linking units in the gel due to such specific interaction. Reversible gel swelling/deswelling and drug permeation changes occurs by the utilization of the difference in association constants between polymerized antibodies and naturally derived antibodies towards specific antigens[5,7,10,11,13].

3. Externally Regulated System

a)Magnetic induces release:

Magnetically regulated system contains magnetic beads in the implant. Magnetic steel beads were engrafted in an ethylene and vinyl acetate (EVAc) copolymer matrix that was loaded with bovine serum albumin as a model drug. The beads oscillate within the matrix on exposure to the magnetic field, alternatively creating compressive and tensile forces. This in turn acts as a pump to push more amount of the active solute out of the matrix [1, 2,3,16].

b)Ultrasound induces release:

Ultrasound is used as an enhancer for the improvement of drug permeation through a biological barrier, such as skin, lungs, intestinal controlled drug delivery e.g. Miyazaki et al. used ultrasound to achieve up to a 27-fold increase in the release of 5-fluorouracil from an ethylene and vinyl acetate (EVAc) matrix. As degradation of biodegradable matrix was enhanced by ultrasonic exposure, the rate of drug release also increased. Increasing the strength of the ultrasound resulted in a proportional increase in the amount of 5- fluorouracil released[1, 2,3,16].

c)Electric field induces release

As these devices use polyelectrolyte thus are pHresponsive as well as electro responsive. Polyelectrolyte contains polymers with comparatively high concentration of ionisable groups along the backbone chain. For chronotherapy, several

technologies are required such as microelectronics and micromachining and potential etc. These technologies also include iontophoresis, iontophoresis and infusion pumps. Under the influence of electric field, electro-responsive hydro gels generally bend, depending on the shape of the gel which lies parallel to the electrodes whereas deswelling occurs when the hydro gel lies perpendicular to the electrodes [1, 2,3,15]

d)Light induces release:

In this system drug delivery is regulated by the interaction between light and material and can be achieved by combining a material that absorbs light at a desired wavelength and a material that uses energy from the absorbed light to regulate drug delivery. A new class of optically active nanoparticles is developed such as Gold nanoshells which comprise of a thin layer of gold surrounding a core. Required composite material can be obtained by implanting the nano shells in a NIPAAm-co-AAM hydro gel. A nanoshell when absorb the near-infrared light and convert it to heat and then temperature of composite hydro gel is raised above its lower critical solution temperature (LCST). Finally, hydro gel collapses and these results in an enhanced rate of release of soluble drug held within the matrix [1, 3, 14, 10.]

SOME NOVEL MULTIPARTICULATE DRUG TECHNOLOGIES

PRODAS Technology **(Programmable Oral Drug Absorption System)**

PRODAS technology is a combination of both Multiparticulate and hydrophilic matrix tablet technologies in which a number of minitablets gathered in a hard gelatine capsule. The minitablets produced by direct compression of granules having active ingredients. As it combines the advantages of tabletting technology within a capsule so it may be immediate release, delayed-release and/or controlled-release drug delivery systems in single dosage form 12,18,19,20.

OROS Technology **(Osmotic-controlled Release Oral delivery System)**

This technology depends on osmotic pressure to give pre-programmed, controlled drug delivery to the gastrointestinal tract. The system is composed of two compartments—the drug vessel and the osmotic engine cap. When the system comes in contact with an aqueous medium, water permeates into the osmotic engine cap through rate-controlling membrane. Hydration of the osmotic engine leads to its expansion, which exerts a driving force against the ridge of the drug vessel. The two compartments separate from each other by sliding apart. After disengaging, the open mouth of the drug vessel is exposed to the fluid environment. Essential entire dose get delivered by Chronoset. The vessel is made of water-impermeable ethylene-co-vinyl acetate copolymer (EVA) and the cap is made of proprietary water-permeable blends of polycaprolactone (TONE) and flux enhancers [12.]

Available marketed products

• Alpress LP (prazosin)
• Covera-HS (verapamil)

Procardia XL (nifedipine)

CODAS Technology **(Chronotherapeutic Oral Drug Absorption System)**

This technology is designed to delay drug release for a predetermined time to tune therapy to the body's circadian rhythms. Again, the technology is based on polymer coated Multiparticulate. The release controlling coating is a blend of water soluble and water insoluble polymers. When water from the gastrointestinal tract get in touch with the polymer coated beads, the water soluble polymer gradually dissolves and the drug diffuses through the resulting pores in the coating. The water insoluble polymer continues to act as a barrier maintaining the controlled release of drug. [18, 19]

Marketed Preparation

Verelan PM XL capsule API- Verapamil HCl

DIFFUCAPS Technology

DIFFUCAPS technology delivers drugs into the body in a circadian release manner. Diffucaps technology in its simplistic form involves the preparation of 12, 18, 20, 21.

(1) Core of Inert particles surrounded by drug layer.

(2) Customized release (CR) beads by coating immediate release (IR) particles with one or more functional dissolution rate (release) controlling polymers or waxes (outermost layer in Figure 10).

(3) One or more functional polymer coated Diffucaps bead populations get combine into hard gelatine or Hydroxypropyl Methylcellulose (HPMC) capsules.

A layer of organic acid or alkaline buffer surrounds the beads to direct solubility of a poorly soluble drug by creating an optimal pH microenvironment (Figure 11). Every Diffucaps bead has an inert core enclosed by drug as well as coated with a functional polymer membrane to control the rate of drug release. The active core may be produced by granulating and milling and/or by extrusion and spheronization of

API.This technology is particularly suitable for drugs that conventionally need multiple daily doses or drugs require customized release formulations. Diffucaps can also be combined with other proprietary Pharmaceutical Technologies to optimize drug delivery[12, 20].

Marketed preparation

• Innopran XL Tablets Verapamil HCl
• Zofran Tablets Ondansetron HCl dehydrate

SODAS Technology **(Spheroidal Oral Drug Absorption System)**

SODAS is a Multiparticulate technology that enables the production of customized dosage forms and responds directly to individual drug candidate needs. The drug loaded beads are coated with controlled release polymers (water soluble and insoluble, pH dependent or independent) to form a release rate controlling membrane. Then, the beads are filled into hard gelatine capsules for ease of administration [18-21.]

Recent Advances In The Pulsatile Drug Delivery System

At present, pulsatile drug delivery systems have great importance in various disease conditions specifically in diabetes where dose is suggested at different time intervals. The sub-systems, multi-particulate systems (e.g. pellets) offer various advantages over single unit. The release profile of pellets can be of any type like time dependent, pH dependent, micro flora activated system. Great interest is taken in site and time specific oral drug delivery to improve therapeutic efficacy. Gastro retentive drug delivery system is a suggestion to prolong gastric residence time, thereby targeting site-specific drug release in upper gastrointestinal (GI) tract. Floating drug delivery system (FDDS) and bio adhesive drug delivery are widely used techniques for gastro retention. Various pulsatile technologies have been developed on the basis of methodologies as discussed previously.

ACCU-BREAK Technology

This technology is designed to easily divisible tablets in exact smaller doses, thus dosage adjustment become easy. In ACCU-T-CR Trilayer tablets, tablet contains a controlled-release (CR) medication and/or immediate release (IR) component. It gets separated by a drug-free break layer which allows the CR dose to be divided into exact half doses [18].

TMDS Technology

The Time Multiple Action Delivery System provides control release rate of multiple ingredients within a single tablet [18].

GEOCLOCK Technology

In this technology, chronotherapy focused presscoated tablets are used in which an active drug remain surrounded by an outer tablet layer consists of a mixture of hydrophobic wax and brittle material. In this way a pH independent lag time is obtained. E.g. **LODOTRA** – used in rheumatoid arthritis [18].

DUREDAS **Technology (Dual Release Drug Absorption System)**

In this technology, a bilayer tablet was manufactured. One layer of the tablets provided with immediate release action and second layer with sustained release action [19].

KV/24

In this technology, one or more drug compounds remain encapsulated to express release of drug in a pre-determined fashion. Prior to coating with one or more polymers, a neutral core is coated with a drug substance to achieve a once-a day release profile. The drug can be combined in two ways, one with the neutral core second incorporated into the coating process [20].

INNOHERB

In this technology, pellets are coated inside of the capsule. Desired active herbal compound converted into micro pellets or small beads. The coating of these carried out by semi permeable membrane to improve stability and mask taste/smell [20].

IPDAS Technology **(Intestinal Protective Drug Absorption System)**

In this, the beads with high density drug are compressed to form controlled release tablets. It is particularly suitable for tablet that cause gastroirritation and disintegrates rapidly. The release is controlled by the nature of the drug-containing bead matrix or its semi-permeable membrane coating. It is extruded and spheronised Multiparticulate based technology. Initially, it was developed for a proprietary formulation of naproxen with fast onset of action to relief pain over a 24-hour period which is marketed in the US and Canada under the trade name Naprelan. [18-21]

ORBEXA Technology

In this multi particulate system, high drug is loaded and product is subjected to granulation. After granulation/extrusion and spheronization, functional polymer membranes are used to coat the resultant

beads for additional release rate control and may be filled into capsules. This technology can be used for sensitive drugs such as proteins. [18-21]

Advantages of Orbexa^{TM} Technology

- ***Aqueous or solvent-based granulation***
- ***High-speed process is well suited for sensitive molecules like proteins***
- ***Suitable for high drug loading.***

Table 2: Marketed Products Of Pulsatile Drug Delivery System [1-6]

Technology	Proprietary name	API	Mechanism and dosage form	Indication
CODAS®	Verelan® PM	Verapamil HCl	Extended release capsule	Hypertension
CONTIN®	Uniphyl®	Theophylline	Extended release tablet	Asthma
OROS®	Covera- HS®	Verapamil HCl	Extended release tablet	Hypertension
DIFFUCAPS ®	Innopran®XL	Propranolol HCl,Verapamil HCl	Extended release capsule	Hypertension
OROS®	Invega™	Paliperidone	Tablet	Schizophrenia
PULSYS™	Pulsincap™	Dofetilide	Rupturable system	Antiarrhythmic
OROS®	Concerta®	Methylphenidate HCl	Tablet	Anti-psychotic
PULSYS™	Moxatag™	Amoxicillin	Multiparticulate system	Infection
TIMERx®	OPANA®	Oxymorphone	Erodible/ soluble barriercoating ER Tablets	Pain management
CEFORM®	Cardiazem® tablet	Diltiazem HCl,Verapamil HCl	Extended Release tablet	Hypertension
Physico-chemical modificationo f API	Pepcid®,	Famotidine	Tablet	Ulce
Physico-chemical modificationo f API	Zocor®	Simvastatin	Tablet	Hypercholesterolemi a
PROCARDI A XL®	Procardia XL	Nifedipine	Sustained release	Hypertension

CURRENT SCENARIO AND FUTURE SCOPE

Now a day's, in the field of drug delivery, more focused is done on the potential of systems that are able to release drugs after a programmable lag phase i.e. in a pulsatile mode. Beside these systems, multiparticulate systems (e.g. pellets) offer several advantages over single unit .In addition to this, there are no risk of dose dumping, flexibility of blending units with different release patterns, as well as short and reproducible gastric residence time.

The future of chronotherapeutics and delivering drugs in a pulsatile manner seems to be quite promising as in certain diseases states. It exhibit several advantages over the traditional zero or first order drug delivery mechanism. Time controlled or site specific single or multiple units are obtained by pulsatile drug delivery techniques. Pulsatile release (time site or specific) most often is achieved by using different polymers in coating layers or by changing the coating thickness.

Conclusion

Although sustained and controlled drug delivery systems have acquired a lot of success and application in field of Pharmacy. These systems are not able to deliver drug according to circadian behaviour of diseases but pulsatile systems have importance in this regard. Due to their high efficiency and lack of undesirable adverse effects to the whole body, the stimuli-responsive feature of these systems is useful for treatment of patients. But major

drawbacks arise from the biological variations among individuals. The basic parameters in the design of polymer based pulsatile systems are the biocompatibility and the toxicity of the polymers used. For successful development of chronotherapeutic dosage form, knowledge of circadian time structure, rhythm in disease pathophysiology or 24 hour pattern in symptom intensity of chronic medical conditions and chronopharmacology of medicationis needed. Significant progress has been made towards achieving pulsatile drug delivery system that can effectively treat diseases with non-constant dosing therapy.It can be concluded that Pulsatile drug delivery system provide a unique way of delivering drugs possessing chronopharmacological behaviour, extensive first pass metabolism, necessity of night time dosing, or absorption window in GIT. Pulsatile drug delivery system shall be promising in future.

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