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# THE REVIEW ON PULSATILE DRUG DELIVERY SYSTEM

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**Abstract:**
*Pulsatile drug delivery systems (PDDS) are gaining importance as they deliver a drug at specific time as per the pathophysiological need of the disease, resulting in improved therapeutic efficacy as well as compliance. Diseases wherein PDDS are promising include asthma, peptic ulcer, cardiovascular diseases, arthritis, attention deficit syndrome in children, and hypercholesterolemia. These delivery systems can be classified into time controlled wherein the drug release is governed primarily by the delivery system; stimuli induced in which release is controlled by a stimuli, like the pH or enzymes present in the intestinal tract or enzymes present in the drug delivery system and externally regulated system where release is programmed by external stimuli like magnetism, ultrasound, electrical effect and irradiation. The current article focuses on the review of literature concerning the disease requiring PDDS, methodologies involved in the existing systems, recent update and product currently available in the market.*
*Key words: Lag time, pulsatile release, multiple unit-systems, chronotherapy, regulatory aspect*

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## INTRODUCTION:

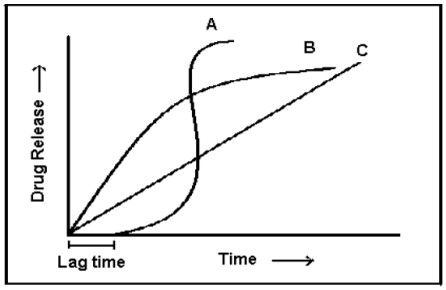
With the advancement of the technologies in the pharmaceutical field, drug delivery systems have drawn an increasing interest over the last few decades. Nowadays, the emphasis of pharmaceutical galenic research is turned towards the development of more efficacious drug delivery systems with already existing molecule rather going for new drug discovery because of the inherent hurdles posed in drug discovery and development process [1].Traditionally, drug delivery has meant forgetting a simple chemical absorbed predictably from the gut or from the site of injection. The oral controlled release system shows a typical pattern of drug release fig.1in which the drug concentration is maintained in the therapeutic window for a prolonged period of time (sustained release), thereby ensuring sustained therapeutic action.

A second-generation drug delivery goal has been the perfection of continuous, constant rate delivery of bioactive agents. However, living organisms are not ‘‘zero-order’’ in their requirement or response to drugs. They are predictable resonating dynamic circadian cycle which will maximize desired and minimize undesired drug effects [2]. fig.2. Till early nineties efforts have been made to design thedrug delivery system which will release the drug at fairly constant rate. In fact these systems turned to be one of the most successful systems in delivering thedrug molecule [3]. But still for many of the drugs, useof such systems is not suitable because of a number of reasons. This is particularly true in cases where thedrug is subjected to large metabolic degradation. Due to ‘first pass effect’ there will be reduction in thebioavailability of the drug because, gradual release can result in greater degradation. Secondly drugs with short half-life need to be administered repeatedly which results in patient non-compliance. Further, in case of chronic treatment, where the drug is given in sustained release dosage form, continuous exposure of the drug to body may lead to adverse effect. For example, diabetes mellitus requires chronic treatment with sustained release formulations of drugs like sulfonylurea which will damage the pancreas earlier than the corresponding immediate release dosage form. Lastly, drugs which exhibit tolerance should not be delivered at a constant rate, since the drug effect decreases with time at constant drug level. In addition drug toxicity increases with time when drug levels are held constant. In such cases it is preferable to opt for dosage form which will provide desired concentration of drug at particular time point only [4].Nowadays, concept of chronopharmaceutics has emerged, wherein, research is devoted to the design and evaluation of drug delivery systems that release a therapeutic agent at a rhythm that ideally matches the biological requirement of a given disease therapy [2].

### Drug release profile of pulsatile drug delivery system

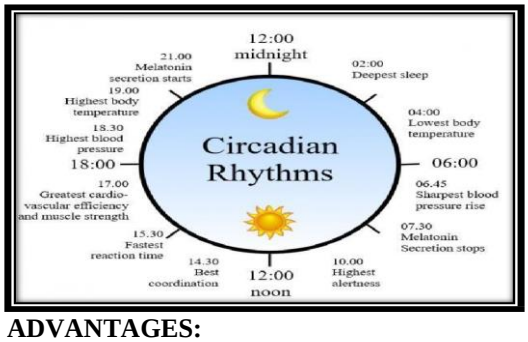
Diseases where a constant drug level are not preferred, but needs a pulse of therapeutic concentration in a periodic manner acts asa push for the development of “Pulsatile Drug Delivery Systems [5]”. In these systems, there is rapid and transient release of a certain amount of drug molecules within a short time-period immediately after a predetermined off release period. **fig. 3.**Various techniques are available for the pulsatile delivery like pH dependent systems, time dependent

systems, micro-flora activated systems, etc. which can be designed as per the physiology of disease and properties of the drug molecule. The focus of the present review is primarily on the pulsatile drug delivery methodologies and the upcoming technologies, which are being exploited on an industrial scale.




Drug release profiles: (A) Pulsatile, (B) Conventional and (C) Extended release.

### ADVANTAGES AND DRAWBACKS OF PULSATILE DRUG DELIVERY SYSTEMS:




### ADVANTAGES:

- Predictable, reproducible and short gastric residence time
- Less inter- and intra-subject variability
- Improve bioavailability
- Reduced adverse effects and improved

tolerability
- Limited risk of local irritation
- No risk of dose dumping
- Flexibility in design
- Improve stability
- Improve patient comfort and compliance
- Achieve a unique release pattern
- Extend patent protection, globalize product,and overcome competition

**DRAWBACKS:**

- Lack of manufacturing reproducibility andefficacy
- Large number of process variables
- Multiple formulation steps
- Higher cost of production
- Need of advanced technology
- Trained/skilled personal needed formanufacturing

**DISEASES REQUIRING PULSATILE DRUGDELIVERY:**

**Diseases following the circadian rhythm in human body**

Thorough understanding of the disease physiologyis required before designing the pulsatile drug delivery system. A disease where rhythmic circadian organization of the body plays an important role, pharmacokinetics and/or pharmacodynamics of the drugs is not constant within 24 h. Table1 enumerates various diseases showing such a chronological behavior. 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 case of cardiovascular diseases, several functions (e.g. BP, heart rate, stroke volume, cardiac output, blood flow) of the cardiovascular system are subject to circadian rhythms.

For instance, capillary resistance and vascular reactivity are higher in the morning and decrease later in the day. Platelet aggregability is increased and fibrinolytic activity is decreased in the morning, leading to a state of relative hypercoagulability of the blood [7]. Circadian variations of glucose and insulin in diabetes have been extensively studied and their clinical.

**Table 1: Diseases requiring Pulsatile Drug Delivery:**

| 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 | β2agonist, Antihistaminic |
| Cardiovascular diseases | BP is at its lowest during the sleep cycle and rises steeply during the early morning awakening period | Nitroglycerin, Calcium channel blockers, 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 |
| Hyper cholesterolemia | Cholesterol synthesis is generally higher during night than during day time | HMG CoA reductase inhibitors |

**POLYMERS USED IN PULSATILE DRUG DELIVERY SYSTEM:**

Pulsatile drug delivery systems are required.Pulsatile drug delivery systems are required for applications in which the continuous release of a drug would be detrimental and repeated dosing would be difficult, painful or otherwise problematic. A key example is insulin delivery for the treatment of diabetes. For effective management, insulin release levels need to be generally very low but significantly elevated after meals. Additional examples of the desirability of pulsatile drug delivery include the delivery of blood pressure medications and immunization boosters, and many hormone treatments. Pumps have been successfully used for pulsatile drug delivery and are now used for many diabetic patients. However, these suffer from a number of limitations, most notably the need to run tubing across the skin, which produces pathways for infection. Completely implantable systems would reduce this risk. The system proposed by Langer and co-workers exploits the wide tailor ability of biodegradation of the poly (lactic-*co*-glycolic acid) (PLGA) family of biocompatible polyesters. By varying the relative amounts of lactic acid and glycolic acid in the copolymer and also the molecular weight of the copolymer, one can controllably and widely vary the degradation rate of the material. To release bursts of drug at different times, several PLGA .
allow the drug to escape. With this system, Langer and colleagues were able to achieve pulsatile release of several types of 'model drugs' with different properties. The drug-delivery system is based on a microchip formed from poly (Llactic acid), the most slowly degrading of this polyester family.

Several reservoirs were indented in the chip surface; drug solutions were microinjected into the appropriate reservoirs, and then PLGA membranes of various compositions were formed to seal each reservoir. Reservoirs could all contain the same drug, or multiple agents could be loaded into different reservoirs to release a variety of drugs from the device. One could envisage an implantable microchip that would release a battery of childhood immunizations at appropriate times. Such a system would be especially useful in developing countries, where routine access to medical care is difficult and thus booster immunizations are often missed. Furthermore, because the drug molecules are stored in a reservoir rather than suspended in the polymer formulation, this system should be compatible with a wide variety of drugs. For example, heparin – a common anti- coagulant that is hydrophilic bioactive after incorporation into and in response to demand. Ideally, such systems will eventually be coupled to biosensor devices so that drug delivery can respond to physiological cues in real time. The release of insulin from an implant could be tied to readings from a glucose sensor, thus providing tighter control over blood glucose levels and reducing the effects of diabetes. Drug release from polymeric systems could be controlled through externally generated the ultrasonic energy can be safely applied from outside the body and can be generated with a small, portable probe. In another example, composites of thermally responsive polymers with nanoparticles that absorb in the near infrared have been shown to undergo marked phase changes in response to near-infrared light. This might be useful as a drug delivery system that releases the drug upon external illumination from a light source similar in size to a laser pointer. These stimuli- responsive systems are likely to offer greater control and flexibility than systems based on inherent differences in polymer degradation, but they will also be more complicated and costly. The potential benefits of pulsatile dosing regimens for a variety of conditions should ensure a high level of interest in modulated drug delivery systems well into the future, and advances in materials science will significantly improve our capabilities in this field of drug delivery

**Methodologies for pulsatile drug delivery**

Methodologies for the pulsatile drug delivery system can be broadly class

**Time controlled PulsatileRelease**
**Single Unit System**
**Multi Particulate System**
**Stimuli – induced**
**Thermo – responsive pulsatile release**
**Chemical stimuli induced Pulsatile systems**
**External stimuli pulsatile release**
**Pulsatile release systems for vaccines and hormoneproducts** [10]

**Time controlled Pulsatile Release System**

The time controlled systems can be classified as single unit (e.g. tablets and capsules) or multiple unit systems.

**Single unit Systems**
**Capsular Systems**

A variety of single – unit PDDS have been developed. A general layout of such systems consists of an insoluble capsule body consisting of a drug and a plug. This plug is removed after a pre- determined lag time due to swelling, erosion or dissolution, they

used spray dried lactose and microcrystalline cellulose in drug core and then core was coated with swelling polymer croscarmellose sodium and an outer . Pulsincap system is a good example of such a system which is made up of such a system that is made up of a water – insoluble body filled with drug formulation.

[11] The body has a closed and an open- end closed with a swellable hydrogel plug. This plug, when comesin contact of the dissolution medium or gastro – intestinal fluids, gets swollen up, and pushes itself out of the capsule after a time lag, which is followed by a spontaneous release of the drug. The time lag can be

controlled by the manipulation of the dimensions and position of the plug. Inclusion of effervescent agents or disintegrants ensures a spontaneous release is case of water insoluble drugs. The plug material consists of insoluble but permeable and swellable polymers [12- 13] (e.g. polymethacrylates), erodible compressed polymers (Polyvinyl alcohol, polyethylene oxide), congealed melted polymers (saturated polyglycolated glycerides), controlled erodible polymer .(pectin). These formations are well tolerated in animals and healthy volunteers, and there are no reports of gastro – intestinal irritation. The problem of gastric residence time has been overcome by enteric coating the system to allow its dissolution only in the higher pH region of small intestine.

**Port Systems**

This system consists of gelatine capsule coated with a semi permeable membrane (e.g. cellulose acetate) along with an insoluble plug (e.g. lipidic). It also contains an osmotically active agent along with the drug formulation [14]. In presence of an aqueous medium, the water diffuses across the semi-permeable membrane, leading to increased inner pressure that ejects the plug after predetermined time lag. The lag time can be controlled by the thickness of the semi permeable membrane. This system shows a good correlation b/w lag time of in- vitro and in-vivo experiments in human beings. [15].An osmotically driven capsular system was developed to deliver the drug in liquid form. In this system, the liquid drug is absorbed into highly porous particles. These particles release the drug through an orifice of semi – permeablecapsule supported by an expanding osmotic layer after the dissolution of the barrier layer. [16] The wall of the capsule is made up of an elastic material and also possesses an orifice. Due to osmosis, there is an increase in the pressure inside the capsule, resulting in stretching of the wall. As the orifice in very minute, there is no flow of drug when the elastic wall relaxes. But as the wall stretches, the orifice also expands sufficiently enough for the release of the drug at a required rate. Styrene – butadiene is one of the suggested elastomers.

**Delivery by a series of stops**

This system is described specifically for the implantable capsules. Here, the capsule consists of a drug along with a water- absorptive osmotic engine which are placed in different compartments separated by a movable partition.

**Pulsatile system based on rupturable coating**

These are multiparticulate systems in which the drug is coated on non- partial sugar seeds followed by a swellable layer and an insoluble top layer coating (Ueda et at 1994). The swelling agents used include super disintegrants like sodium carboxymethyl cellulose, sodium starch glycollate and polymers like polyvinyl acetate, polyacrylic acid, polyethylene glycoletc. Effervescent system comprising a mixture of tartaric acid, citric acid and sodium bicarbonate may also be used alternatively. Upon entrance or ingress of water, the expansion of swellable layer takes place leading to rupture of film with the subsequent rapid drug release. The environmental factors like pH and drug solubility do not affect the release of drug at all. Variation in coating thickness or addition of high amounts of lipophilic plasticizer in the outermost layer can lead to variation in the lag time. With increase in concentration of osmotic agent, a rapid release after the lag phase can be achieved. [26] [27]

**Time controlled expulsion system**

This system is based on a combination of osmotic and swelling factors. The core consists of the drug, a low bulk density solid and/or liquid lipid material (e.g. mineral oil) and a disintegrant also. The core further contains a coating of cellulose acetate. When immersed in an aqueous medium, the water penetrates the core and displaces the lipid material [28]. Subsequently, an increase in internal pressure takes place resulting in rupturing of the coating material. This system is also known as Osmotic based rupturable coating system. Another system is based on a capsule or tablet composed of a large no. of pellets with different releasepattern. [29] The core consists of the therapeutic drug and a water soluble osmotic agent in each pellet. The core is enclosed by water – permeable, water insoluble polymer film. The polymer film is incorporated with a hydrophobic, water insoluble agent that alters the permeability (e.g. wax, fatty acid or a salt of fatty

acid). The film coating of each population differs from another pellet coating due to water influx and drugefflux . The rate of drug diffusion is regulated by theswelling of pellets due to the dissolution of osmotic agent . A single dosage form provides a series of pulsesas each pellet population releases its drug content. Thissystem was used for the delivery of anti- hypertensive drug diltiazem.Also, some osmotically active agents are used that do not undergo swelling. These pellet cores consist of drug along with sodium chloridecoated with semi-permeable cellulose acetate polymer. The coat is selectively permeable to water and is impermeable to the drug. The presence of sodium hydroxide produces fast release of drug while its absence gives sustained release after the lag time. [30]

**Pulsatile Delivery by change in Membrane Permeability**

The presence of different counter–ions in the medium can influence the permeability and water uptake of acrylic polymers with quaternary ammonium groups [31]. Several delivery systems based on this ion exchange have been developed. Eudragit is a polymer of choice for this purpose [32]. It contains positively polarized quaternary ammonium group in the polymer side chain, that are always accompanied by negative hydrochloride counter ions. As the ammonium group is hydrophilic, it facilitates the interaction of polymer with water and thereby changes its permeability and allows the water to permeate the active core in a controlled manner. This property is essential to achieve precisely defined lag time. Theophylline, was used as model drug with sodium acetate used to prepare the cores. These pellets were coated using Eudragit (10% to 40% weight gain) in 4 different layer thicknesses. A correlation b/w film thickness and lag time was observed. The permeability of the eudragit film was affected dramatically even with a small amount of sodium acetate in the pellet core. After the lag time, theinteraction between acetate and polymer increases the permeability of the coating such that the entire dose is liberated within a few minutes. [31] The lag increases with increasing thickness of the coat, but the release of drug was not affected by this thickness and dependedon the amount of salt present in the system.

**Sigmoidal Release System**

This system comprises of pellet core containing drug and succinic acid coated with ammonia – methacrylate copolymer. [33] The permeability of the film is enhanced by the drug inside and the acid solution. The water in the medium dissolves Succinic acid. In place of succinic acid, acetic acid, glutaric acid, tartaric acid, malic acid and citric acid is also used. This system was used to design an acid containing core.(Narisowa et at. 1994,1996

**Stimuli induced 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.

**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. Y.H. Bae et al developed indomethacin pulsatile release pattern in the temperature ranges between 200 C and 300 C by using reversible swelling properties of copolymers of N-isopropylacrylamide and butyrylacrylamide. 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

**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 there by decreasing the insulin release. Examples of the pH sensitive polymers include N, N dimethylaminoethyl methacrylate, chitosan, polyol etc. Obaidat and Park prepared a copolymer of acryl amide and allyl glucose. The side chain glucose units in the copolymer were bound to concanavalin A. These

hydrogels showed a glucose-responsive, sol–gel phase transition dependent upon the external glucose concentration. Okano et al developed the system based upon the fact that boronic acid moiety forms reversible bonds with polyol compounds including glucose [54]. They used water-soluble copolymers, containing phenylboronic acid side chains which showed formation of a reversible complex gels with polyol compounds such as poly(vinyl alcohol) (PVA). Such complexes dissociated after the addition of glucose in a concentration dependent manner

**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 inflammatoryinduced 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 antiinflammatory drug incorporated HA gels as new implantable drug delivery systems

**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 [56]. Special attention was given to antigenantibody 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.

**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, sodium carboxymethylcellulose. These polymers are used as enteric coating materials so as to provide release of drug in the small intestine. Yang et al developed pH-dependent delivery system of nitrendipine in which they have mixed three kinds of pH dependent microspheres made up of acrylic resins Eudragit E-100, Hydroxypropylmethylcellulose phthalate and Hydroxypropylmethylcellulose acetate succinate as pH dependent polymers. In one of the study carried out by Mastiholimath et al attempt was made to deliver theophylline into colon by taking the advantage of the fact that colon has a lower pH value (6.8) than that of the small intestine So, by using the mixture of the polymers, i.e. Eudragit L and Eudragit S in proper proportion, pH dependent release in the colon was obtained

**External Stimuli Pulsatile release**

These systems are not self – regulating, but instead require externally generated environmental changes to initiate drug delivery. These can include magnetic fields, ultrasound, temperature, light etc.

**Magnetic Field**

Use of an oscillating magnetic field to modulate the rates of drug delivery from a polymer matrix was one of the first methodologies investigated to achieve an externally controlled drug delivery system. [44] Magnetic steel beads were embedded in an ethylene and vinyl acetate (EVAC) copolymer matrix that wasloaded with bovine serum albumin as a model drug.

During exposure to magnetic field, the beads start oscillating within the matrix, therefore creating compressive and tensile forces. These forces act as a pump to push an increased amount of the drug molecule out of the matrix. The co-polymers having higher Young‘s modulus were more resistant to induced motion of steel beads, thereby, magnetic field has less effect on rate of drug release from these materials. Also, different Formulations were developed for in- vitro magnetically triggered delivery of insulin based on alginate spheres. [47]
A treatment method that involves the administration of a magnetic material composition, which contains single-domain magnetic particles attached to a target- specific ligand, to a patient and the application of an alternating magnetic field to

inductively heat the magnetic material composition, which cause the triggered release of therapeutic agents at the target tumour or cancer cells, also exists. [48]

**Ultrasound**

Ultrasound is used for improving drug permeability across biological barriers such as skin, lungs, intestinal wall and blood vessels. Many reports describe the effect of ultrasound on controlled drug delivery. [49- 55] Kost et.at described an ultrasound – enhanced polymer degradation system.

As degradation of biodegradable matrix was enhanced by ultrasonic exposure, the rate of drug release also increased. Therefore, pulsed drug delivery was achieved by the on- off application of ultrasound. [56] Supersaxo et. at also reported macromolecular drug release from biodegradable poly microspheres. A sustained release can be maintained up to a several months. Authors speculated that ultrasonic exposure results in the enhancement of water permeability within microspheres of the polymer matrix, inducing drug dissolution into the releasing media. [57] There was an increase up to 27 times in the release of 5 Fluorouracil from an ethylene and vinyl acetate matrix using Ultrasound. an increase in the strength of ultrasound resulted in a proportional increase of 5 fluorouracil.[58]Increase in the rate of p-nitroaniline from apolyanhydide matrix during ultrasonic irradiation is reported [59]. It was noted that there was an increase in drug delivery was greater than the increase in matrixerosion when the ultrasound triggering was active. therefore, it was hypothesised that acoustic cavitation by ultrasonic irradiation was responsible for the modulated delivery of p-nitroaniline. [50]

**Temperature**

Temperature is most widely utilized stimulus for a variety of pulsatile drug delivery systems. Its use has been justified by the fact that the temperature of human body often deviates from physiological temp i.e. 37$^{o}$c. Bae. Y.H. et. al. developed Indomethacin pulsatile drug delivery system in temperature range between 20-30 degree Celsius by using reversible swelling properties of co polymer of N-isopropylacrylamide and butyryl acrylamide. [60] This deviation can be used as a stimulus that activates the release of the therapeutic agents from various temperature – responsive drug

**Electric Field**

An electric field works as an external stimulus with several advantages like availability of equipment‘s, which allows precise control with regards to the magnitude of current, duration of electric pulses, interval between pulses etc.

The mechanism of drug release chiefly includes ejection of drug from the gel as the fluid phase synereses out, drug diffusion along a concentration gradient, the electrophoresis of charged drug towards an oppositely charged electrodes and liberation of the entrapped drug as the gel complex erodes. [80]

**Pulsatile release systems for vaccine and hormoneproducts**

Vaccines are traditionally administered as an initial shot of an antigen followed by repeated booster shots to produce protective immunity [81]. The frequency of the booster shots and therefore the exact immunization schedule depends on the antigen. Also, co- administration of vaccine adjuvant is given for the enhancement of immune response to achieve protectiveimmunity. [82] PDDS offers 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.

**RECENT ADVANCEMENT IN PDDS:**

Pulsatile-release formulations have many advantages over immediate-release formulations. With these formulations, less frequent drug administration is possible, and patient compliance can correspondingly be improved. In the field of drug delivery, increased attention has recently been focused on the potential of systems that are able to release drugs after a programmable lag phase commencing at administration time, i.e., in a pulsatile mode. During the last two decades, technologies to ensure time-controlled pulsatile release of bioactive compounds have been developed. Significant progress has been made towards achieving pulsatile drug delivery systems that can effectively treat diseases with non-constant dosing therapies, such as diabetes. However, there is much work that needs to be carefully demonstrated for the pulsatile delivery of bioactive compounds, especially hormones31.

**CONCLUSION:**

Circadian rhythm of the body is an important concept for understanding the optimum need of drug in the body. There is a constant need for new delivery systems that can provide increased therapeutic benefits to the patients. Pulsatile drug delivery is one such system that, by delivering drug at the right time, right

place and in right amounts, holds good promises of benefit to the patients suffering from chronic problems like arthritis, asthma, hypertension etc. 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 ofpulsatile drug delivery systems, should ensure thatthe current high level of interest inthis area would stretch wellinto future and ensures the betterment of quality life

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