PULSATILE DRUG DELIVERY SYSTEM: A BOON IN PATIENT COMPLIANCE

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ABSTRACT
Pulsatile system is gaining a lot of interest as it is increasing patient compliance by means of providing time and site specific drug delivery system. A pharmaceutical dosage form is capable of delivering the drug into the body in a time controlled pulsatile release fashion, is composed of a multitude of multicoated particulate (beads, pallets, or granules). Drugs which exhibit tolerance should not be delivered at constant rate since the drug effect become less with the passage of time at constant drug level. Drug toxicity also increases with time when levels are held constant. In such cases it is preferable to go for a drug delivery which will provide desired concentration of drug at particular time point only. A delivery system with release profile that is characterized by time period of no release(lag time) followed by a rapid and complete drug release(pulse release) can be called as an ideal pulsatile drug delivery system. Many diseases which follow circadian rhythm like arthritis, asthma, cardiovascular disorders, cancer, hypcholesterolemia are well cured by pulsatile drug delivery system. Different methodologies are being used to prepare pulsatile systems like time dependent, externally regulated (magnetically activated, photo sensitive and electrically stimulated), as well as stimulated systems (pH dependent, temperature dependent) etc. Recent advances in the field of pulsatile drug delivery like CODAS®, DIFFUCAPS®, and TIMER® are highly demanded in these days.

KEYWORDS: Pulsatile release, chronotherapeutics, time controlled systems, lag time, rupturable coating.

INTRODUCTION
The oral controlled-release system shows a typical pattern of drug release in which the drug concentration is maintained in the therapeutic window for a prolonged period of time, thereby ensuring sustained therapeutic action. In this system ‘tolerance’ problem can be noticed so it is not suitable for all diseases e.g. drug 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. Recent studies have revealed that diseases have a predictable cyclic rhythm and that the timing of medication regimens can improve the outcome of a desired effect. This condition demands release of drug as a “pulse” after a time lag and such system has to be designed in a way that complete and rapid drug release should follow the lag time. Such systems are known as pulsatile drug delivery systems (PDSS).1,2 Pulsatile drug delivery is of the chief types of the novel drug delivery system. It aims to release drugs on a planned pattern i.e. at suitable time and/or at proper site of action. There are many other modern systems which deliver the drug at predetermined rate with unremitting release like controlled release and sustained release but sometimes these kind of drug delivery show tolerance problem /dilemma for certain medication that is why pulsatile drug delivery is preferred to overcome this difficulty. Pulsatile drug delivery system is the one that follow circadian rhythm, an biological clock which is directly related to many physiological as well as pathological conditions of the body. There are many diseases which show circadian rhythm like heart attack, asthma, arthritis etc that call for such a system that must show it’s effect at the exposure time of disease symptoms.3

Example: Inflammation symptoms associated with joint pain in night as in arthritis. To get rid of this problem, a dose should be given during day time to avoid night pain provided maximum release at night hours and this is only and only possible by pulsatile drug delivery system. The main motive of this system is to maintain the pharmacological response and to inhibit the serious incidence of undesired side effects.3 The pulsatile drug delivery presents the relationship between performances of a delivery system with internal functioning of human body which introduces a new therapy known as ‘chronopharmacotherapy’. It is based on the circadian
rhythm of body. This delivery is quite different from the present day delivery systems depend on homogeneous release.

Pulsatile drug delivery systems which can be administered via the oral route are divided into two major categories as

1- Time controlled drug delivery system
2- Site specific delivery system

In time controlled drug delivery system the drug is released following the lag phase, matching the human circadian rhythm. Multiunit , multilayer with different combination of immediate and sustained release preparations come under this category.\(^1^{,}2^{,}3\)

**Concept of lag time in pulsatile drug delivery system**
Definition of lag time

“Lag time is defined as the time between when a dosage form is placed into an aqueous environment and the time at which the active ingredient begins to get released from the dosage form.”

- A lag time of at least 0.5 hr or longer is considered to be important while a lag time of less than it is of little significance.
- Lag times of more than 4 hrs are desired for delivery of drug into lower portion of small intestine while lag times between 0.5 and 4 hr are desirable in drug delivery in upper regions of gastrointestinal tract.\(^4\)

The lag time prior to the rupturable membrane is mainly controlled by

1- The permeation and mechanical properties of the polymer coating.
2- The swelling behavior of the swelling layer.

As it is often found in the living body, many crucial functions are regulated by pulsed or transient release of bioactive substances at specific site and time thus it is significant to develop new drug delivery system to achieve pulsed delivery of a certain amount of drugs in order to mimic the function of living body. Therefore this type of drug delivery is such system that by delivering medicament at accurate time, exact place and right amounts holds good promises of assistance to the patients suffering from chronic disorders like arthritis and asthma. The site specific systems are controlled by pH of target site, enzymes present in intestinal tract, transient time and pressure of various parts of the intestine.

**There are many conditions that demand pulsatile release like**\(^5\)

- In certain body functions that follow circadian rhythm, e.g secretion of hormones, acid secretion in stomach, gastric emptying
- Chronopharmacotherapy of diseases: bronchial asthma, myocardial infarction, angina pectoris, rheumatic disease, ulcer, and hypertension.
- Drugs that produce biological tolerance demand for a system that will prevent their continuous presence at the biophase.
- The lag time is essential for the drugs that undergo degradation in gastric acidic medium (e.g: peptide drugs) and irritate the gastric mucosa or induce nausea and vomiting.
- Targeting a drug to distal organs of gastro-intestinal tract (GIT) like the colon requires that the drug release is prevented in the upper two-third portion of the GIT.
- The drugs that exhibit:
  - First-pass metabolism
  - Reduced bioavailability
  - Altered steady state levels of drug and metabolite,
  - Food drug interactions.

**Advantages on drugs**\(^6\)

A pulsatile drug release in which the drug is released completely, after a well-defined lag time without continuous drug release, is advantageous for the following drugs or therapies:

- An extensive first-pass metabolism of drugs, e.g., beta-blockers, could be overcome by saturation of metabolic enzymes with pulses of high peak levels instead of constant drug flow below the saturation threshold.
- By avoiding the constant presence of the drug, to which patients develop biological tolerance, at the site of action.
- Drug targeting a specific site in the intestinal tract, e.g., to the large intestine or to the colon for the treatment of inflammatory diseases.
- Protection of the gastric or upper intestinal mucosa from irritating drugs

**Advantages and drawbacks of pulsatile drug delivery systems**\(^7\)

**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 and efficacy
- Large number of process variables
- Multiple formulation steps
- Higher cost of production
- Need of advanced technology
- Trained/skilled personal needed for manufacturing

**Diseases required pulsatile**[1]

<table>
<thead>
<tr>
<th>Disease</th>
<th>Chronological behavior</th>
<th>Drug used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peptic ulcer</td>
<td>Acid secretion is high in afternoon and at night</td>
<td>H2 blockers</td>
</tr>
<tr>
<td>Asthma</td>
<td>Attacks during night and in morning hour</td>
<td>(\beta) agonist, antihistaminics</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>BP is lowest in sleeping cycle and rises in early morning</td>
<td>Nitroglycerin, calcium channel blockers,</td>
</tr>
<tr>
<td>Arthritis</td>
<td>Pain in the morning and more pain in night</td>
<td>NSAIDs, Glucocorticoids</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Increase in blood sugar level after meal</td>
<td>Sulphonylurea, Insulin, Biguanide</td>
</tr>
<tr>
<td>Attention deficit syndrome</td>
<td>Increase in DOPA level in afternoon</td>
<td>Methylphenidate</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>Cholesterol synthesis is higher in night than during day</td>
<td>HMG CoA reductase inhibitors</td>
</tr>
</tbody>
</table>

(Table 1)

**CHRONOPHARMACOLOGY**

The study of variations in the drug response as influenced by the time is known as chronopharmacology. There are certain conditions which demand release of drug after a lag time i.e., Chronopharmacotherapy of diseases which shows Circadian rhythms in their pathophysiology. These circadian changes are due to hormones changes in body. A number of hormones, such as renin, aldosterone, or cortisol, show distinct daily fluctuations. Circadian rhythm regulates many body functions in humans, viz., metabolism, physiology, behaviour, sleep patterns, hormone production, etc.[10]

It has been reported that more shocks and heart attacks occur during morning hours. The level of cortisol is higher in the morning hours, and its release is reported to decline gradually during the day.

Eg: Patients suffering from osteoarthritis are reported to have less pain in the morning than night, while patients suffering from rheumatoid arthritis feel more pain in the morning hours. Various diseases like asthma, hypertension, acidity, and arthritis show circadian variation, that demands time scheduled drug release for effective drug action.

Drug pharmacokinetics too show circadian variation for anti-inflammatory drugs like indomethacin, ketoprofen and diclofenac sodium which have greater absorption in morning as compared to evening, and site-specific absorption from small intestine. Therefore, to develop dosage form for chronopharmacotherapy the desired drug release should be time-specific as well as site-specific also.[11]

Now, the concept of “**chronopharmaceutics**” has emerged, wherein, research is performed to design and evaluation of drug delivery system that release a therapeutic agent at the rhythm that ideally matches the biological requirement of a given disease therapy.

‘Chronopharmaceutics” is made up of 2 words
- Chronobiology
- Pharmacetics

Pharmacetics deals with the dosage form designing, their store and evaluation.

There are three types of mechanism rhythms in our body
1- Circadian
2- Ultradian
3- Infradian

1- Circadian- it comes from latin word “circa” means ‘about’ and “dies” means ‘day’.
2- Ultradian- oscillations of shorter duration are known as ultradian (more than one cycle per 24 hrs)
3- Infradian- oscillations that are longer than 24 hrs are known as infradian. (less than one cycle per day)[12]

**Types of Pulsatile Drug Delivery**

**Single unit system**

**Capsular system**

Single unit systems are mostly developed in capsule form. The lag time is continued by a plug, which gets pushed away by swelling or erosion, and the drug is released as a pulse from the insoluble capsule body. e.g.: Pulsincap system.[13] In this system a water insoluble body containing the drug formulation, system is closed with a swellable hydrogel, plugged at open end. Upon contact with, gastrointestinal fluid or dissolution medium the plug swells pushing itself out of the capsule after lag-time. For rapid release of water insoluble drug effervescent or disintegrating agents are added.

![Figure 1: Design of Pulsincap system](image-url)
Plug material is generally made up of following:
Swellable materials coated with but permeable polymer (polymethacrylates).
Erodible compressed polymer (HPMC, polyvinyl alcohol).
Congealed melted polymer (glyceryl mono oleate).
Enzymatically controlled erodible polymer (pectin).

Pulsatile delivery by osmosis
This system consists of a capsule coated with a semi permeable membrane. Inside the capsule was an insoluble plug consisting of osmotically active agent and the drug formulation. This system shows good invivo and invitro correlation in humans and used to deliver methylphenidate to school age children for the treatment of Attention Deficit Hyper activity Disorder (ADHD).

Pulsatile delivery by solubilisation or erosion of membrane

The programmable oral release technology (PORT system) is a good example of osmosis based pulsatile drug delivery. This consists of a gelatin capsule coated with a semi permeable membrane (e.g., cellulose acetate) covering an insoluble plug (e.g., lipidic) and an osmotically active agent along with the drug formulation. When in contact with the aqueous medium, water diffuses across the semipermeable membrane, resulting in increased inner pressure that ejects the plug after a lag time. The lag time is controlled by coating thickness.\textsuperscript{[15,16]}

Pulsatile delivery by rupturable coating

In this system drug reservoir is surrounded with a soluble or erodible barrier layer that dissolves with time and the drug releases at once after the lag time, e.g., Time Clock system. The Time Clock system consists of solid dosage form coated with lipid barriers such as carnauba wax & beeswax along with surfactants like polyoxyethylene sorbitan monooleate. The system contacts the aqueous medium resulting in coat emulsification or erodes after the lag-time depending on the thickness of coat. The lag time of system independent of the gastrointestinal motility, PH, enzyme & gastric residence.\textsuperscript{[17-21]}

Pulsatile delivery by rupture of membrane
These systems are based up on a reservoir system coated with a rupturable membrane. The outer membrane ruptures due to the pressure developed by effervescent agents or swelling agent. Citric acid & sodium bicarbonate is added as effervescent mixture in tablet core coated with ethyl cellulose, when system comes in contact with water it produces carbon dioxide gas which exerts pressure & after lag time rupture the membrane & rapid release of drug occurs.

Multiple Unit Systems
Multiparticulate systems are reservoir type of devices with a coating, which either ruptures or changes its permeability. Drug is coated over sugar seeds these granules may then be packaged in a capsule or compressed with additional excipients to form a tablet. The active pharmaceutical ingredient may also be blended or granulated with polymers before coating to provide an additional level of control. However, drug loading in this type of system is low due to higher need of excipients.\textsuperscript{[25]}

Pulsatile delivery by rupturable coating
Similar to single unit system, the rupturing effect is achieved by coating the individual units with
effervescent or swelling agents. Drug delivery was controlled by the rupture of the membrane. The timing of release was controlled by the thickness of coating and the amount of water soluble polymer to achieve the pulsed release. The swelling agent includes superdisintegrants like carboxy methylcellulose, sodium starch glycollate. Polymers like polyacrylic acid, polyethylene glycol etc. and tartaric acid & sodium bicarbonate that used as effervescent agent. 

2. Stimuli induced pulsatile systems
This system works on the basis of biological stimuli like temperatue or any chemical stimuli. The drug is released after the exposure of any chemical produced within the body or temperatue. These systems are further classified in to temperature induced systems and chemical stimuli induced system.\[34\]

2.1 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.\[35\]

2.2. Chemical stimuli induced Pulsatile systems\[36\]
2.2.1. Glucose-responsive insulin release devices
In diabetes mellitus the increment in body glucose level is noticed with the decrement in insulin supply as well, so timely injections are given to control sugar level. A number of systems have been developed which are able to do changes in glucose concentration. One such system includes pH sensitive hydrogel containing glucose oxidase immobilized in the hydrogel. When glucose concentration in the blood increases glucose oxidase converts glucose into gluconic acid which changes the pH of the system. This pH change induces swelling of the polymer which results in insulin release. Insulin by virtue of its action reduces blood glucose level and consequently gluconic acid level also gets decreased and system turns to the deswelling mode thereby decreasing the insulin release. Examples of the pH sensitive polymers includes N,N-dimethylaminoethyl methacrylate, chitosan, polyl etc.\[37\]

2.2.2. 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. 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.\[38\]

2.2.3. Drug release from intelligent gels responding to antibody concentration
There are numerous kinds of bioactive compounds which exist in the body. Recently, novel gels were developed which responded to the change in concentration of bioactive compounds to alter their swelling/deswelling characteristics. Special attention was given to antigen-antibody complex formation as the cross-linking units in the gel, since such interaction 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.\[39\]

Methodologies for pulsatile drug delivery
Methodologies for the pulsatile drug delivery system can be broadly classified into three classes;
1. Time controlled
2. Stimuli induced
3. Externally regulated

1. Time controlled pulsatile release system
In time controlled drug delivery systems pulsatile release is made after a specific time interval in order to mimic the circadian rhythm of body.
Various methodologies that can be used for time controlled pulsatile release systems are discussed in following section.
- Delivery systems with rupturable coating layer
- Delivery systems provided with erodible coating layers
- Capsule shaped system provided with release controlling plug\[31\]

Capsule shaped system provided with release controlling plug
These systems contain release controlling plug between immediate release compartment and pulsed release compartment. On contact with aqueous fluids, the cap rapidly dissolves thereby releasing the immediate release component followed by pulsed release component. The lag time is provided by the plug which is inserted in to the body.\[31,32,33\]
2.2.4. 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. By selecting the pH dependent polymers drug release at specific location can be obtained. Examples of pH dependent polymers includes 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. [40]

3. Externally regulated systems

For releasing the drug in a pulsatile manner, another way can be the externally regulated systems in which drug release is programmed by external stimuli like magnetism, ultrasound, electrical effect and irradiation. Magnetically regulated system contain magnetic beads in the implant. On application of the magnetic field, drug release occurs because of magnetic beads. [41]

Magnetically stimulated

In an experiment, ferrite microparticulates(1µm) and insulin powder were dispersed in sodium alginate solution. The ferrite-insulin alginate suspension was then added to aqueous calcium chloride solution drop wise which cause the cross linking in the form of alginate spheres. The alginate spheres were further cross linked with aqueous solution of poly(l-lysine) or poly(ethylene amine). Magnetic field characterestics due to ferrite microparticulate and the machenical properties of polymer matrix play a role in controlling the release rate of insulin from the system. [42]

Ultrasoundically stimulated

Drug permeation through skin, lungs, intestinal wall and blood vessels can be enhanced by the use of ultrasound effect. Ultrasound enhanced polymer degradation facilitates the drug molecules release from system by repeated ultrasonic exposure thus the rate of drug release is increased. in this, pulse delivery is gained by the on-off application of ultrasound. [43]

Photo stimulated

This can be achieved by combining a material that absorbs the light at desired wave length and a material which uses the energy of absorbed light to effect the drug delivery. When nano shells are embedded in NIPA Am-co-AAM hydrogel formed the required material and exposed to near infrared light, nanoshells absorbs the light and convert it into heat, increasing the temperature of composite hydrogel. This results into the increased rate release of drug from matrix system. [44]

Electrically stimulated

Electrically responsive delivery systems are prepared from polyelectrolytes and thus pH responsive as well as electro responsive. Under the influence of electric field electro responsive hydrogel deswell, swell or erode. Poly (2-acrylamine-2-methyl propape sulfonic acid-co-butyl methacrylate) hydrogels were used for electric stimulated drug delivery. This rapid, squeezing effect and electro osmosis of the gel. [45]

Diseases to be controlled by pulsatile drug delivery system

Rheumatoid arthritis

The chronologial behavior of rheumatoid arthritis has been studied carefully. For instance, there is circadian rhythm in the plasma concentration of C-reactive protein and interleukin-6 of the patient suffering from RA. The victims of RA feels more pain in morning but less in night while in osteoarthritis, the conditions are quite different. In osteoarthritis, pain is at its highest level in night which decreases during day time. Different NSAIDs are used to curb the joint pain. [46,47]

Pulmonary disease

In the pathogenesis and treatment of asthma, circadian rhythm plays a vital role. In the case of this disease, the airway resistance increases at night and reaches a low point in the early morning hours. the therapy of asthma has been suggested with corticosteroids, theophylline and β2 agonists. [48,49]

Hypercholesterolemia

Many circadian alterations in lipid fraction in the normal as well as in patients, can cause the changes in the metabolism rhythm and in the blood coagulation system, thus carry out many complications. A circadian rhythm is followed in hepatic cholesterol synthesis which is generally high during day. Treatment with HMG Co reductase inhibitors has recommended that evening dosing was more effective than morning dosing. [50,51,52]

Diabetes mellitus

The circadian changes of glucose and insulin in diabetes have been studied and their clinical importance in the case of insulin substitution in type 1 diabetes has been studied. The main aim of insulin therapy is to mimic the normal physiologic pattern of endogenous insulin secretion. [53,54]

Gastro-intestinal disorders

The functions of GIT are effected by circadian rhythm. Gastric acid secretion is highest at night, while gastric motility so the disintegration, dissolution and absorption of drug is also slow at night. Therefore, for effective gastric ulcer, once daily at bed time has been suggested for an H2 antagonist. [55]

CVS disease

Many functions of CVS like blood pressure, cardiac output, stroke volume, blood flow of cardiovascular system are influenced by circadian rhythm. BP is lower during sleeping time and rises steeply during the early morning. Platelet aggregation is increased so the fibrinolytic activity is decreased in the morning, thus cause hypercoagulability of blood. [56,57]
Cancer
Recent studies on human beings and animals have suggested that anticancer drug administration at carefully predetermined time may be more beneficial and less toxic in the chemotherapy of cancer. The blood flow of tumors was threefold greater during each daily activity phase of circadian cycle than during the daily rest phase. The chronotherapy concept develops a revolution in the field of oncology.\textsuperscript{[58,59]}

Colonic delivery
Colon is the most suitable site for drug absorption as low proteolytic enzyme activity is found there. It is good for delivering protein and peptide drugs. Colon specific drug delivery prevent the drug release in stomach and small intestine, and affect an onset of drug release upon entry into colon. Time dependent delivery is a mean of targeting the drug load after a pre-programmed time delay. The time is difficult to predict in advance, although a lag time of 5 hours is usually considered sufficient, given that small intestine transit time is reported to be relatively constant at 3 to 4 hours.\textsuperscript{[60]}

Preparation and evaluation of pulsatile drug delivery system\textsuperscript{[61]}
- Preparation of solid dispersion: Drug was dispersed in mannitol and heated till mannitol liquifies, The dispersion is cooled and dispersion was scrapped out using a spatula
- Preparation of alginate beads: Sodium alginate was dissolved in distilled water with agitation to have different concentrations of 1, 2, 3, 4, 5, 6 (w/v). The drug as solid dispersion was added to this solution, then the drug suspension was added to solution contain CaCl\textsubscript{2} with different concentration to cure for 15 min. The drug dispersion was added drop wise into this solution using a microsyringe (16 guage). After the beads were formed the beads were separated, washed with distilled water, dried in air for 48th and the diameters of 50 beads were randomly measured under optical microscope and averaged.
- Treatment of capsules with formaldehyde: Bodies of hard gelatin cap placed in formaldehyde (15%) in a dessicator & KMnO\textsubscript{4} was added until vapours were produced.\textsuperscript{[70]}The reaction was carried out for 12hrs & dried at 50 degree c for 30 min to ensure completion of reaction. Then dried at room temp.
- Filling of capsules: Pellets were incorporated in to capsule & plugged with HPMC, guar gum, CMC sod, sod alginate separately at concentration of 20 mg, 30 mg, 40 mg.
- Coating of capsule with enteric resistant polymer: Cap were coated with cellulose acetate phthalate to prevent gastric emptying. All formulations were assayed to determine drug content & to check the ability to provide colon specific drug delivery in buffer pH 1.2 for 2 hr, pH 7.4 for 3 hr, & pH 6.8 for 7 hr.
- Modification of enteric coating: Coating with CAP were repeated until an 8-12% increase in weight. Percent weight gain of capsule before & after coating was determined.
- Evaluation of pulsincap
  - Characterization of powder: The carr’s index & angel of repose study were conducted and reported.
  - \textit{In vitro disintegration test:} 10 Capsules were randomly selected then subjected to disintegration at room temperature in buffer of pH 1.2, 7.4, 6.8. Time taken by each capsule was recorded.
  - \textit{Moisture uptake study:} Capsule were exposed to different humidity condition and the effect were compiled and accordingly reported.
  - \textit{Buoyancy test:} The obtained beads were studied for buoyancy and floating time using USP XXIII type 2 dissolution test apparatus. One hundred beads of each batch were placed in 900 ml of 0.1 N HCl (pH 1.2) containing 0.02% w/v Tween 80 and agitated at100 rpm, temperature was maintained at 37 C ± 2. Number of sinking beads was observed visually.
  - \textit{In vitro release study:} It is carried out for 12 hrs for both the plain drug pellete & the modified pulsincap dosage form acc to USP apparatus 1 basket method\textsuperscript{[70]}The media were used as acidic buffer pH 1.2 for 2 h, phosphate buffer pH 7.4 for 3 hr & pH 6.8 buffer for subsequent hr at 50 rpm Equal volume of media was replaced immediately, filtered & diluted Amount of diclofenac was determined by UV absorption at 273 nm & 277 for acidic & basic media.
  - \textit{Surface characterization:} Surface morphology of pellets was studied using SEM after coated with gold vapours, at different magnification.
  - \textit{Stability studies:} The optimized formulation would be subjected to stability studies as per ICH guideline for tropical countries.
  - \textit{Analysis of data:} The data obtained will be subjected to different statistical test for envisaging the result of the prepared delivery system.

Recent advances
At the present time pulsatile drug delivery system is progressing with a very high speed. There are different types of this delivery system but multi particulate system provides more benefits as compare to single unit system. Drug targeting in upper gastrointestinal tract is also possible by the development of gastro retentive drug delivery system. Other recent approaches in pulsatile drug delivery system are Floating and Bioadhesive drug delivery system. Advancis Pharmaceutical Corp., German town, Maryland, USA has developed once-a-day pulsatile delivery system called PULSYS\textsuperscript{®}, this system enables the delivery of antibiotic amoxicillin in regular concomitant pulsates. CODAS\textsuperscript{®} (Verapamil HCl) tablet, DIFFUCAPS\textsuperscript{®} (Propranolol HCl) capsules, TIMERx\textsuperscript{®} (Oxymorphone) tablet, are some new techniques to develop pulsatile system.\textsuperscript{[70]}
TIMEX®, Geminex® and SyncroDoseTM (Penwest Pharmaceuticals and Co., USA) was developed. The TIMEX® oral drug delivery system achieves a variety of release profiles (first order, zero order, burst release, etc.) for a wide range of drugs, accommodating even the most difficult actives. CODAS® (Elan Drug Technologies) as multiparticulate pH dependent system, for delivery of verapamil HCl (Verelan® PM) in form of extended release capsule. This delay in release is introduced by the level of release—a controlling polymer applied to the drug-loaded beads. Diffucaps® (Eurand Pharmaceutical, Vandalia, Ohio.) technology is a multiparticulate system that the water-insoluble and enteric polymers are molecularly dispersed in the lag-time coating membrane, for chronotherapeutic delivery of a combination of two drugs. Pulsincap® (R. P. Scherer International Corporation, Michigan, US) is one such system that comprises of a water-insoluble capsule enclosing the drug reservoir. A swellable hydrogel plug was used to seal the drug contents into the capsule body.\[7][2]

CONCLUSION
Pulsatile drug delivery system has been realized as an extremely useful system in various scientific areas. Over the years, many methodologies have been employed for developing pulsatile drug delivery system like controlled PDDS which is often made up of rupturable or erodible polymer coating layer. This system is critically needed as traditional formulations cannot cope up with diseases with chronological pathophysiology so pulsatile drug delivery is of assistance. The future holds a lot of promises in pulsatile drug delivery system and by further study this will be developed as novel and efficient approach. There is a constant need for new delivery systems that can provide increased therapeutic benefits to the patients. Circadian rhythm of the body is an important concept for understanding the optimum need of drug in the body. Thus, designing of proper pulsatile drug delivery will enhance the patient compliance, optimum drug delivery to the target side & minimizing the undesired effects. Multiparticulate system exhibits decrement in dose dumping problem and enhancement in different release pattern. This unique system may be of any type like time dependent, pH dependent and micro flora activated system.

Conflict of Interest
There is no conflict of interest between authors.

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