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A REVIEW ON THE PULSATILE DRUG DELIVERY SYSTEM FOR CIRCADIAN RHYTHM

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ABSTRACT

Traditionally, the drugs are release in an immediate or extended fashion. However, in the recent years, the pulsatile drug release systems are increasing developing interest. This framework is designed for chronopharmacotherapy which are based on the circadian rhythm. The rationale for the employment of pulsatile release is for drugs where a constant drug release, i.e., zero-order release is not desired. Pulsatile drug delivery system (PDDS) is defined as the rapid and transient release of the certain amount of molecules within a short time period immediately after a predetermined off-release period, i.e., lag time. PDDS can be classified into the time controlled systems wherein the dug release is controlled primarily by the delivery systems; stimuli induced PDDS is in which release is controlled by the 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. Therefore, Pulsatile drug delivery is one such system that, by delivering the drug at the right time, right place and in the right amount, holds good promises of benefit to the patients suffering from chronic problems like arthritis, asthma, peptic ulcer, cardiovascular diseases, and hypercholesterolemia. Current review article focuses on the necessity of pulsatile drug delivery systems, types of the disease in which pulsatile release is required, classifications, evaluations, advantages, limitations and future aspects of the pulsatile drug delivery system.

KEYWORDS: Pulsatile drug release, Circadian rhythm, Chronopharmacotherapy, Lag time, Time controlled systems.

I. INTRODUCTION

PULSATILE DRUG DELIVERY SYSTEM

Pulsatile drug delivery is defined as the rapid and transient release of certain amount of active molecules within a short time period immediately after a predetermined off released period, i.e., lag time, or these systems have a peculiar mechanism of delivering the drug rapidly and completely after a lag time, i.e., a period of no drug release. Such a release pattern is known as pulsatile release.[1] Pulsatile drug delivery systems (PDDS) have attracted attraction because of their multiple benefits over conventional dosage forms. They deliver the drug at the right time, at the right site of action and in the right amount that 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 rapidly and completely as a pulse after a lag time. These products follow the sigmoid release profile characterised by a time period. These systems are beneficial for the drugs with chronopharmacological behavior, where nocturnal dosing is needed, and for drugs that show the first-pass effect.[2]

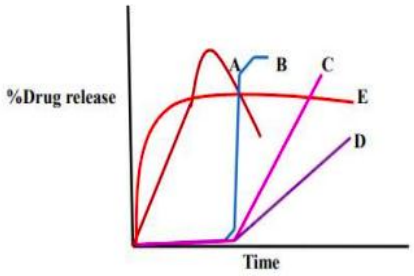


Fig.1: Drug release profiles from pulsatile drug delivery system.

Where, A: Conventional release profile, B: Burst release of drug as a after a lag time, C: Delayed release profile after a lag time, D: Constant release profile in prolonged period after a lag time, E: Extended release profile without lag time. Circadian rhythm regulates many body functions in the humans, viz., metabolism, physiology, behaviour, sleep patterns, hormone production, etc. 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. Blood pressure is also reported to be high in the morning till late afternoon, and then

drops off during night. 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 The release of some drugs is preferred in pulses. A single dosage form provides an 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.

NECESSITY OF PULSATILE DRUG DELIVERY SYSTEMS

There are many conditions and diseases where sustained release formulations don't show good efficiency. In such cases Pulsatile Drug Delivery System is applicable.

1. First pass metabolism in Some drugs, like beta blockers, and salicylamide, undergo extensive first pass metabolism and require fast drug input to saturatemetabolizing 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 often 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 periods 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.

ADVANTAGES

- Predictable, reproducible and short gastric residence time.
- Less inter-and intra-subject variability.
- Improves bioavailability.
- Reduced adverse effects and improved tolerability.
- Limited risk of local irritation.
- No risk of dose dumping.
- Flexibility in design.
- Ease of combining pellets with different compositions or release patterns
- Improves stability.
- Improves patient comfort and compliance.
- Achieves a unique release pattern.[3]

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 professionals.[4]

LIMITATIONS

Pulsatile drug deleivery systems have certain limitation, so in many cases these drug delivery system is fails,[5-7]

• Multiple manufacturing steps in case of Multiparticulate pulsatile drug delivery system.
• Low drug load
• Incomplete release
• In-vivo variability in single unit pulsatile drug delivery system.

Chrono-therapeutics

refers to a therapy in which In vivo availability of drug is timed to match rhythms of disease or disorders in order to improve therapeutic responses and minimize side effects, which makes it a profound and purposeful delivery of medications in unequal amounts over time (during the 24 h). Chronotherapeutics takes into account rhythm determinants of the human circadian time structure to determine the drug-delivery pattern, dose, and administration time to optimize desired and/or minimize adverse effects.[8 -11]

BIOLOGICAL RHYTHMS

1. Ultradian Rhythms: Oscillations of shorter span are termed Ultradian Rhythms (more than one cycle per 24 h). E.g.90 minutes sleep cycle.

2. Infradian Rhythms: Oscillations that are longer than 24 hours are named as Infradian Rhythms (less than one cycle per 24hours).

E.g. Monthly Menstruation.

3. Circadian rhythms: Circadian rhythms are self-sustaining, endogenous oscillations that occur with a periodicity of about 24 Hours and regulate many body functions like-metabolism, sleep pattern, hormone production etc. Several physiological processes in humans vary in a rhythmic manner, in synchrony with the internal biological clock.[12]

II. CLASSIFICATION OF PULSATILE DRUG DELIVERY SYSTEM

Various approaches of pulsatile drug: Pulsatile drug delivery system can be broadly classified into three classes.

1. Time controlled pulsatile drug delivery
2. Stimuli induced pulsatile drug delivery
3. Externally regulated pulsatile drug delivery

1. Time controlled pulsatile drug delivery
A. Single unit pulsatile systems
E.g.Capsule based systems
Pulisincap system
2. Capsular system based on Osmosis a. 'PORT' System
b. System based on expandable orifice
c. Delivery by series of stops.
d. Pulsatile delivery by solubility modulation
3. Pulsatile system with Erodible or soluble barrier coatings.
a. The chronotropic system
b. 'TIME CLOCK' System.

c. Compressed tablets
d. Multilayered Tablets
4. Pulsatile system with rupturable coating
B. Multiparticulate / Multiple unit systems:
1. Pulsatile system with rupturable coating
E.g. Time –controlled Explosion system (TCES)
2. Osmotic based rupturable coating system
E.g. Permeability controlled system
3. Pulsatile delivery by change in membrane permeability
E.g. Sigmoidal release system.

SINGLE-UNIT SYSTEMS

Capsular systems: Different single-unit capsular pulsatile drug delivery systems have been developed. A general structure of such systems consists of an insoluble capsule body housing a drug and a plug. The plug is removed after a predetermined lag time owing to swelling, erosion, or dissolution. The Pulsincap® system shown in fig. 4 (Scherer DDS, Ltd) is an example of such a system that is made up of a water-insoluble capsule body filled with drug formulation. The body is closed at the open end with a swellable hydrogel plug. Upon contact with dissolution medium or gastro-intestinal fluids, the plug swells, pushing itself out of the capsule after a lag time. This is followed by a rapid drug release. The lag time can be controlled by manipulating the dimension and the position of the plug. For water-insoluble drugs, a rapid release can be ensured by inclusion of effervescent agents or disintegrants. The plug material consists of insoluble but permeable and swellable polymers (e.g., polymethacrylates), erodible compressed polymers (e.g., hydroxypropylmethyl cellulose, polyvinyl alcohol, polyethylene oxide), congealed melted polymers (e.g., saturated polyglycolated glycerides, glyceryl monooleate), and enzymatically controlled erodible polymer (e.g., pectin). These formulations were well tolerated in animals and healthy volunteers, and there were no reports of gastrointestinal irritation. However, there was a potential problem of variable gastric residence time, which was overcome by enteric coating the system to allow its dissolution only in the higher pH region of small intestine.[14-16]

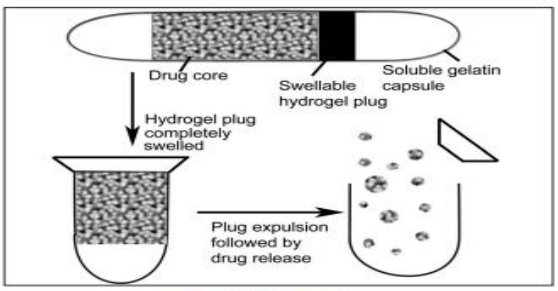


Figure 2: Pulsincap system

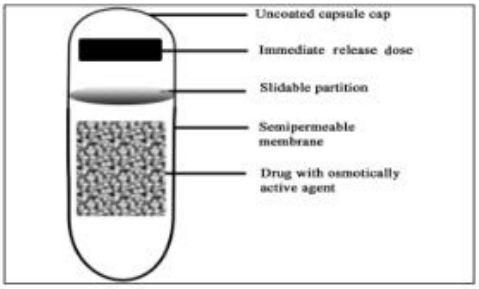


Figure 3: The PORT system

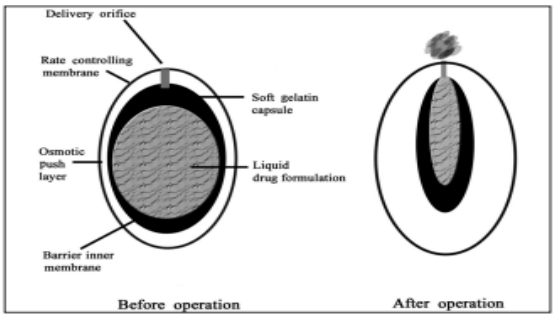


Figure 4: L-OROS Softcap system

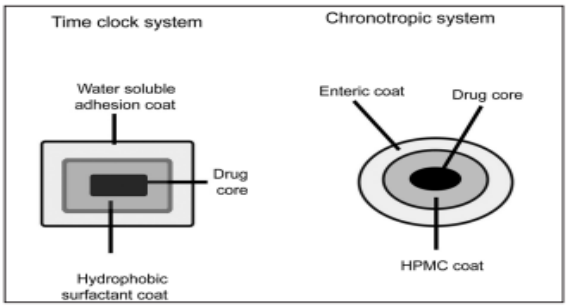


Figure 5: Time clock and chronotropic systems

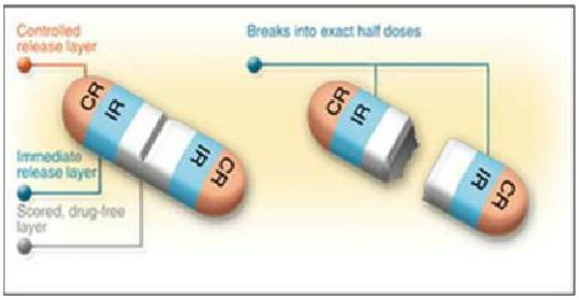
Capsular System Based on Osmosis

The Port® System shown in Drug release mechanism from PORT system is shown in fig. (Port Systems, LLC) consists of a gelatin capsule coated with a semipermeable membrane (e.g., cellulose acetate) housing 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. The system showed good correlation in lag times of invitro and in-vivo experiments in humans. The system was proposed to deliver methylphenidate for the treatment of attention deficit hyperactivity disorder (ADHD) in school-age children. Such a system avoids a second daily dose that otherwise would have been administered by a nurse during school hours.[17-20]

Multilayered Tablet

A release pattern with two pulses was obtained from a three-layered tablet containing two drug containing

layers separated by a drug-free gellable polymeric barrier layer. This three-layered tablet was coated on three sides with in impermeable ethyl cellulose, and the top portion was left uncoated. Upon contact with dissolution medium, the initial dose incorporated into the top layer was released rapidly from the noncoated surface. The second pulse was obtained from the bottom layer after the gelling barrier layer of HPMC was eroded and dissolved. The rate of gelling and/or dissolution of the barrier layer control the appearance of the second pulse. The gelling polymers reported include cellulose derivatives like HPMC, methyl cellulose, or polyvinyl alcohols of various molecular weights and the coating materials include ethyl cellulose, cellulose-acetatepropionate, methacrylic polymers, acrylic and methacrylic co polymers, and polyalcohols.[21][22]



Pulsatile system with Rupturable coating

In contrast to the swellable or erodible coating systems, these systems depend on the disintegration of the coating for the release of drug. The pressure necessary for the rupture of the coating can be achieved by the effervescent excipients, swelling agents, or osmotic pressure fig.11. An effervescent mixture of citric acid and sodium bicarbonate was incorporated in a tablet core coated with ethyl cellulose. The carbon dioxide developed after penetration of water into the core resulted in a pulsatile release of drug after rupture of the coating. The release may depend on the mechanical properties of the coating layer. It is reported that the weak and non-flexible ethyl cellulose film ruptured sufficiently as compared to more flexible films. The lag time increases with increasing coating thickness and increasing hardness of the core tablet. The highly swellable agents, also called super disintegrants, were used to design a capsule-based system comprising a drug, swelling agent, and rupturable polymer layer. Examples of superdisintegrants include cross carmellose, sodium starch glycollate, and low substituted hydroxypropyl cellulose. The swelling of these materials resulted in a complete film rupture followed by rapid drug release. The lag time is function of the composition of the outer polymer layer. The presence of hydrophilic polymer like HPMC reduced the lag time. The system can be used for delivery of both solid and liquid drug formulations. A reservoir system with a semipermeable coating was designed for delivery of drugs that exhibit extensive first-pass metabolism. The release pattern was similar to that obtained after administration of several immediate-release doses.[23][24]

Advantage: Ease of manufacturing.

Disadvantages: In-vivo variability (food effects which is present in G.I.T.).

MULTIPLE - UNIT SYSTEMS

Multiple systems (e.g., pellets, beads) offer various advantages over singleunit 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 drugcarrying capacity of multiple 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.

Pulsatile System Based on Rupturable Coating

Time-Controlled Explosion System: This is a multiple system in which drug is coated on non-pareil sugar seeds followed by a swellable layer and an insoluble top layer. The swelling agents used include superdisintegrants like sodium carboxymethyl cellulose, sodium starch glycollate, Lhydroxypropyl 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. The lag time can be varied by varying coating thickness or adding high amounts of lipophilic plasticizer in the outermost layer. A rapid release after the lag phase was achieved with increased concentration of osmotic agent. Invivo studies of time-controlled explosion system (TCES) with an in-vitro lag time of three hours showed appearance of drug in blood after 3 hours, and maximum blood levels after 5 hours.[25-26]

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 disintegrant was prepared. This core was then coated with cellulose acetate. Upon immersion in aqueous medium, water penetrates the core displacing lipid material. After the depletion of lipid material, internal pressure increases until a critical stress is reached, which results in rupture of coating. Another system is based on a capsule or tablet composed of a large number of pellets consisting of two or more pellets or parts (e.g., populations). Each pellet has a corethat contains the therapeutic drug and a watersoluble osmotic agent. Water-permeable, 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. The use of osmotically active agents that do not undergo swelling was reported by Schultz and Kleinebudde. 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 coreswelling that resulted in generation of small fissures.[27]

Pulsatile delivery system 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 RS30D (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 sosignificantly 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 and depended on the amount of salt present in the system.[28]

Sigmoidal Release System: This consists of pellet cores comprising drug and succinic acid coated with ammonio-methacrylate copolymer USP/NF type B. The lag time is controlled by the rate of water influx through the polymer membrane. The water dissolves succinic acid, and the drug in the core and the acid solution in turn increases permeability of the hydrated polymer film. In addition to succinic acid, acetic acid, glutaric acid, tartaric acid, malic acid, or citric acid can be used. The increased permeability can be explained by improved hydration of film, which increases free volume. These findings were used to design a coated delivery system with an acid containing core. The invitro lag time correlated well with in-vivo data when tested in beagle dogs.[29-54]

RECENT ADVANCES IN THE PULSATILE DRUG DELIVERY[55-56]

Nowadays pulsatile drug delivery systems are gaining importance in numerous disease conditions specifically in diabetes whereever dose is needed at different time intervals. Among these systems, multi-particulate systems (e.g. pellets) offer numerous benefits over single unit that include no risk of dose dumping, flexibility of blending units with different release patterns, as well as short and reproducible gastric residence time.

Multiparticulate systems consists pellets of various release profile which might be of any type like time dependent, pH dependent, micro flora activated system as discussed in the previous sections. Site and time specific oral drug delivery have recently been of great interest in pharmaceutical field to attain improved therapeutic efficacy. Gastroretentive drug delivery system is an approach to prolong gastric residence time, thereby targeting sitespecific drug release in upper gastrointestinal (GI) tract.

Floating drug delivery system (FDDS) and bioadhesive drug delivery are widely used techniques for gastro retention. Low density porous multiparticulate systems are employed by researchers for formulation of FDDS. Sharma and Pawar developed multiparticulate floating pulsatile drug delivery system using porous calcium silicate and sodium alginate for 74 time and site specific drug release of meloxicam. Various pulsatile technologies have been developed on the basis of methodologies as discussed previously. These includes OROS® technology, CODAS® technology, CEFORM® technology, DIFFUCAPS® technology, Threedimensional printing®, timerx® etc.

Table 2: Marketed Products of Pulsatile Drug Delivery

Technology	API	Disease	Proprietary name
CODAS®	Verapamil Hcl	Hypertension	Verelan® PM
CONTIN®	Theophylline	Asthma	Uniphyl®
CEFORM®	Diltiazem HCl	Hypertension	Cardiazem®
Diffucaps®	Verapamil HCl, Propranolol HCl	Hypertension	Innopran®
Pulsincap®	Metronidazole	Antihelminthic	-
Geoclock™	Prednisone	Rheumatoid arthritis	Lodotra
OROS®	Methylphenidate	Anti-psychotic	Concerta®
PULSYS ™	Amoxicillin	Antibiotic	Moxtag™
Three dimensional printing®	Diclofenac sodium.	Inflammation	Theirform®
TIMERx®	Oxymorphone	Pain management	OPANA®

III. EVALUATION TEST OF PULSATILE DRUG DELIVERY SYSTEM

Preformulation study:[57] Different physicochemical properties of drug and drug in excipient mass are evaluated in Preformulation study.

Drug excipients interaction study: The Fourier transform infrared (FTIR) technique and Differential scanning calorimetry (DSC) can be used to study the physical and chemical interactions between the drug and excipients used.

Evaluation of granule: Prepared granules are evaluated for Angle of Repose, Bulk Density, Tapped Density, Carrs index (or) % Compressibility, Hausner's Ratio.

Tablet Thickness: Thickness of tablet is measured using vernier caliper. Five tablets are selected randomly from individual formulations and thickness is measured using vernier caliper scale. The test is carried out in triplicate**.**

Uniformity of weight:[57] Twenty tablets are taken and their weight is determined individually and collectively on a digital weighing balance. The average weight of one tablet is determined from the collective weight. Not more than two tablets deviate from the percentage given below from the average weight and none deviate by more than twice the percentage shown. The Pharmacopoieal Specification of weight variation is given in following table 4.

Table 3: Weight Uniformity Criteria for tablet.

S.No.	Average weight of tablets(mg)	Percentage deviation
1	80mg or less	±10
2	More than 80mg but less than 250mg	± 7.5
3	250mg or more	±5

Hardness/ Crushing strength:[57] Hardness or tablet crushing strength (fc the force required to break a tablet in a diametric compression) is measured using Monsanto Hardness tester. It is expressed in Kg/cm2. Tablets require certain amount of strength or hardness and resistance to friability, to withstand mechanical shocks of handling in manufacture, packaging, and shipping.

Evaluation of polymeric film (only in film coating approach)[58]

a) Visual evaluation: Casted films are then visually evaluated for Physical properties of film like could be peeled off easily from the plate or not; Appearance of the film formed like smooth-rough surface, oily-non oily, Transparent-Opaque film.

b) Tensile strength: The casted films after drying are then carefully cut into film strips (length 40 mm x width 20 mm) and investigated for tensile strength. The method used for evaluating the mechanical properties is based on guideline. Tensile strength = Breaking Force (F)/ Cross sectional area (A)

c) Folding endurance: The test is carried out to check the efficiency of the plasticizer and strength of the film prepared using varying concentration of the plasticizers. The folding endurance is then measured manually. A strip of film (2 x 2 cm) is cut evenly and repeatedly folded at the same place until it breaks. The number of times counted until film could be folded at the same place without breaking, this is gave the value of folding endurance. The test is carried out in triplicate.

d) Mechanical properties: Polymer films (6.5 X 6.7 cm2) are fixed in a self-designed Teflon holder [59,60] with several holes (diameter 10 mm). Films are fixed by using the holder and optionally immersed into 0.1 N HCl at 37 C for 2 h (wet films). The mechanical properties of the dry and wet films are measured with a puncture test using a Texture analyzer (n = 3). A metal probe with a hemispherical end (diameter 5 mm, length 15 cm) is driven at a speed of 5 mm/min until the film ruptured

force– displacement curves are recorded and following parameters are calculated.
Puncture strength = Fmax/ ACS Where, Fmax is the maximum applied force at film break, ACS is the cross-sectional area of the edge of the film located in the path of the cylindrical hole of the film holder, with ACS = 2rd where r is the radius of the hole in the holder and d is the thickness of the film.

e) In vitro dissolution study:[59-60]
The in vitro dissolution study is performed by using dissolution test given in monograph or in standard literature. In general case, dissolution media are 900 ml of 0.1 M HCl for 2 h (since average gastric emptying time is 2 h) and 900 ml of phosphate buffer pH 6.8 for 3 h (average small intestinal transit time). After 5 h, the dissolution medium is replaced with pH 7.4 phosphate buffer (900 ml) and tested for the drug release up to specific hour dissolution study. At the predetermined time intervals, specific volume of dissolution media (1, 2, 5, 10 ml etc..) are withdrawn, filtered through a 0.45 µm membrane filter, diluted, and assayed at wavelength maxima using a UV spectrophotometer.

F) Comparison of dissolution profiles:[61] The similarity factor (f2) given by SUPAC guidelines for a modified release dosage form is used as a basis to compare the dissolution profiles. The dissolution profiles are considered to be similar when f2 is between 50 and 100. The dissolution profiles of products are compared using f2 which is calculated from the following formula: Where, n is the dissolution time and Rt and Tt are the reference) and test dissolution value at time t.
Kinetic modeling of dissolution data.The dissolution profile of all batches are fitted to various models such as zero order, first order, Higuchi, Hixon Crowell, Korsmeyer and Peppas to ascertain the kinetic of drug release. In vivo study of prepared formulation: [61] The prepared formulation is tested for an in vivo study to check the passage of the dosage form throughout the GIT. The purpose of the in vivo study is to find the location of the capsule during its passage through the GI tract. In this study, drug granules are replaced with barium sulfate. The dosage form is prepared in the similar manner as optimized formulation. The volunteer with overnight fasting is taken for the study. The laxative is given to the volunteer before 12 h of the study to completely empty the GIT content. The X-ray study is performed at 2-h, 3-h, 5-h, and 8-h interval,dissolution medium (mucosalside) into the serosal side (absorption compartment) and is analyzed by a validated analytical method at regular time intervals after filtration through a membrane filter of 0.45 µm pore size.[61]

IV. CURRENT SITUATION AND FUTURE SCOPE
Now a day's the pulsatile drug delivery is gaining popularity. The prime advantage in this drug delivery is that drug is released when necessity comes. As a result the chance of development of drug resistance which is seen in conventional and sustained release formulations is reduced. Furthermore, some anticancer drugs are very toxic. These drugs provide dangerous issues in conventional and sustained release therapies. Currently several Food and Drug Administration approved chronotherapeutic drugs are available in the market. This therapy is principally applicable whereever sustained action isn't needed and drugs are toxic. Key purpose of this formulation is to seek out circadian rhythm i.e. appropriate indicator which can trigger the discharge of drug from the device. Another point is absence of suitable rhythmic biomaterial which should be biodegradable, biocompatible and reversibly responsive to specific biomarkers in rhythmic manner. Regulatory is another big question. In preapproval phase it's typically difficult to show chronotherapeutic advantage in clinical settings. In post approval phase causal recreational drug abuse along with on a much larger scale, by the criminal diversion of these modified formulations for profit have arisen problems. The FDA has now heavily relied on the development and implementation of risk management programs as a strategy to allow an approval of a drug to go forward while exercising some restrictions. Many researches are going on the pulsatile drug delivery to discover circadian rhythm with suitable device in the world. In future this delivery will be a leading way to deliver therapeutic agents due to its some unique characters like low chance of dose dumping, patient compliance and the above factors. [62-66]

CONCLUSION
Pulsatile drug delivery is one such system that, by delivering a drug at right time, right place, and in right amounts, holds good promises of profit to the patients suffering from chronic issues like arthritis, asthma, hypertension, etc. Extended release formulations and immediate release formulation aren't efficient in treating the diseases particularly diseases with chronological pathopysiology, for which, pulsatile drug delivery is helpful. The drug is delivering in this system when its actual concentration is required as per chronological need, so pulsatile release systems should be promising in the future.

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