

The Review on - Pulsatile Drug Delivery Systems.

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ABSTRACT: Pulsatile drug delivery systems (pdds) have attracted attention 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, which provides more benefit than conventional dosages and increased patient compliance. These systems are designed according to the circadian rhythm of the body, and the drug is released rapidly and completely as a pulse after a lag time. These products follow the sigmoid release profile characterized by a time. These systems are beneficial for the drug with chronopharmacological behaviour, where nocturnal dosing is required, and for drugs that show first pass effect. In this review article we discuss about pulsatile drug delivery and its recent terminologies, its major use in non-steroidal anti-inflammatory drugs also we study its applications in controlled drug delivery system and current scenario, approaches according to circadian rhythm and advantages, disadvantages, applications. We discuss whole study about floating system and many more things about pulsatile drug delivery system.

Keywords: chronotherapy, delayed release, lag phase, pulsatile release.

I. INTRODUCTION:

Oral drug delivery is the largest segment of the total drug delivery market. It is the most preferred route for drug administration. The oral controlled-release systems show 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 up to the early nineties, great efforts have been spent in the design of delivery systems able to release active ingredients over an extended time lapse at a theoretically constant rate; in this respect, the principle of homeostasis, has deeply affected the interests and objectives of pharmaceutical scientists. As a result, their research activity has been grounded on the construct according to which all physiological

functions are kept relatively constant in time by inherent mechanisms that are triggered by variations derived from the environment^[3]

Circadian rhythm regulates many body functions in humans, viz., metabolism, physiology, behaviour, sleep patterns, hormone production, etc. It has been reported that more strokes 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^[5]

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. Traditionally, drug delivery has meant for getting a simple chemical absorbed predictably from the gut or from the site of injection. 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 systems, which require different amounts of drug at predictably different times within the circadian cycle which will maximize desired and minimize undesired drug effects^[6].

Over the past three decades, advances in research aiming towards underlying principles to bring both commercial and therapeutic values to health care products, are contributing to novel drug delivery systems. These new and/or improved delivery systems work on various principles by providing variable/constant drug amounts over a particular time period in our body based on the fact that physiologic parameters display constancy over a time, however, a new concept which belie this popular belief, termed as chronotherapy has been introduced, chrono-therapeutics refers to a clinical practice of synchronizing drug delivery in a manner consistent with the body's circadian rhythm including disease states to produce maximum health benefit and minimum harmful effects the dependence of several diseases and body function on circadian rhythm is well known. A genetic control of a "master clock" located in the nucleus suprachiasmatic us has been recently proposed , numerous studies conducted, suggest that pharmacokinetics, drug efficacy and side effects can be modified by following therapy matching the biological rhythm. Specificity in delivering higher amount of drug in a burst at circadian timings correlated with specific pathological disorder is a key factor to achieve maximum drug effect [3–6]. Rhythms in the onset and extent of symptoms were observed in diseases such as, bronchial asthma, myocardial infarction, angina pectoris, rheumatic disease, ulcer, diabetes, attention deficit syndrome, hypercholesterolemia, and hypertension. All these acted as a push for the development of "pulsatile drug delivery systems."^[7]

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 , various techniques are available for the pulsatile delivery, broadly classified as, single-unit and multiple-unit systems. Overall, they work on same basic principles of erosion or dissolution; swelling and rupturing; and system based on change in membrane permeability. However, single unit pulsatile drug delivery system may suffer from the disadvantage of unintentional disintegration of the formulation due to manufacturing deficiency or unusual gastric physiology that may lead to drastically compromised systemic drug bioavailability or loss of local therapeutic action^[4]

The pulsatile effect, i.e., the release of drug as a "pulse" after a lag time must be designed in such a way that a complete and rapid drug release should follow the lag time (fig. 1). Such

systems are also called time-controlled as the drug released is independent of the environment. Pulsatile drug delivery systems are gaining a lot of interest and attention these days. 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." Though most delivery systems are designed for constant drug release over a prolonged period, pulsatile delivery systems are characterized by a programmed drug release, as constant blood levels of a drug may not always be desirable (fig. 1). Pulsatile systems are designed in a manner that the drug is available at the site of action at the right time in the right amount. These systems are beneficial for drugs having high first-pass effect; drugs administered for diseases that follow chrono pharmacological behaviour; drugs having specific absorption site in git, targeting to colon; and cases where night time dosing is required^[4]

Chrono pharmacotherapy

"chrono pharmaceuticals" consist of two words chronobiology and pharmaceuticals.

1. **Pharmaceutics** is the discipline of pharmacy that deals with the process of turning a new chemical entity (nce) into a medication to be used safely and effectively by patients. It is also called the science of dosage form design and deals with the formulation of a pure drug substance into a dosage form.
2. **Chronobiology** is the study of biological rhythms and their mechanisms. There are three types of mechanical rhythms in our body, they are: a) circadian "circa" means about and "dies" means day. B) ultradian oscillation of shorter duration is termed as ultradian (more than 1 cycle per 24 hrs). C) infradian oscillations those are longer than 24 h (less than one cycle per day) [8]

Classification of pdds

1. Based on stimuli induced:

- A. **Temperature induced system:** (thermo responsive pulsatile release) 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 200c and 300c by using reversible swelling properties of copolymers of

isopropylacrylamide and butyrylacrylamide. Kataoka et al developed the thermo sensitive polymeric micelles as drug carrier to treat the cancer. They used endfunctionalized poly (n isopropylacrylamide) (pipaam) to prepare corona of the micelle which showed hydration and dehydration behavior with changing temperature

- B. **Chemically induced system:** there has been much interest in the development of stimuli sensitive delivery systems that release a therapeutic agent in presence of specific chemical moieties like enzyme or protein. One of the good examples is glucose-responsive insulin release devices in which insulin is release on increasing of blood glucose level. In diabetes mellitus there is rhythmic increase in the levels of glucose in the body requiring injection of the insulin at proper time. Several systems have been developed which are able to respond to changes in glucose concentration. One such system includes ph sensitive hydrogel containing glucose oxidase immobilized in the hydrogel. When glucose concentration in the blood increases glucose oxidase converts glucose into gluconic acid which changes the ph of the system. This ph change induces swelling of the polymer which results in insulin release. Insulin by virtue of its action reduces blood glucose level and consequently gluconic acid level also gets decreased and system turns to the deswelling mode thereby decreasing the insulin release
- 2. **External stimuli pulsatile release:** 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.

- A. **Electrically stimulated:** electrically responsive delivery systems are prepared by poly electrolytes (polymers which contain relatively high concentration of ionisable groups along the backbone chain) and are thus, ph-responsive as well as electro responsive. Under the influence of electric field, electro responsive hydrogels generally bend, depending on the shape of the gel which lies parallel to the electrodes whereas deswelling occurs when the hydrogel lies perpendicular to the electrodes.
- B. **Magnetically stimulated:** magnetically regulated system contains magnetic beads in the implant. On application of the magnetic field, drug release occurs because of magnetic beads. Magnetic carriers receive their magnetic response to a magnetic field from incorporated materials in beads such as magnetite, iron, nickel, cobalt etc. Tingyu liu, et al developed the magnetic hydrogels which was successfully fabricated by chemically crosslinking of gelatin hydrogels and fe3o4 nanoparticles (ca. 40–60 nm) through genipin (gp) as cross-linking agent. Saslawski et al. Developed different formulations for in vitro magnetically triggered delivery of insulin based on alginate spheres. In an experiment, ferrite microparticles (1µm) and insulin powder were dispersed in sodium alginate aqueous solution. The ferrite-insulin alginate suspension was later dropped in aqueous calcium chloride solution which causes the formation of cross linked alginate spheres, which were further cross linked with aqueous solution of poly(l-lysine) or poly(ethylene imine).

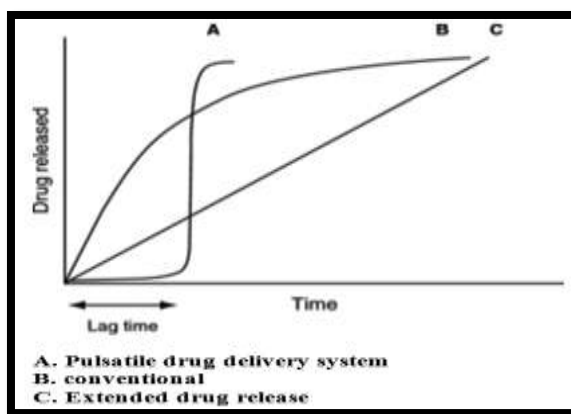
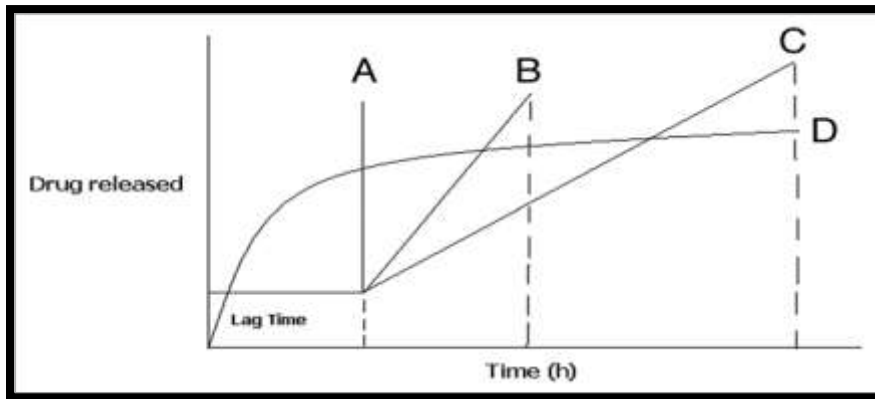


Fig no 1 drug delivery system and release profile [18]



Graph 2. Schematic representation of different drug delivery systems where (a) sigmoidal release after lag time (b) delayed release after lag time (c) sustained release after lag time (d) extended release without lag time.

Classification of pulsatile systems

Pulsatile systems can be classified into single and multiple-unit systems. Single-unit systems are formulated either as capsule-based or osmosis-based systems.

Single unit systems are designed by coating the system either with eroding/soluble or rupturable coating. In multiple unit systems, however, the pulsatile release is induced by changing membrane permeability or by coating with a rupturable membrane.

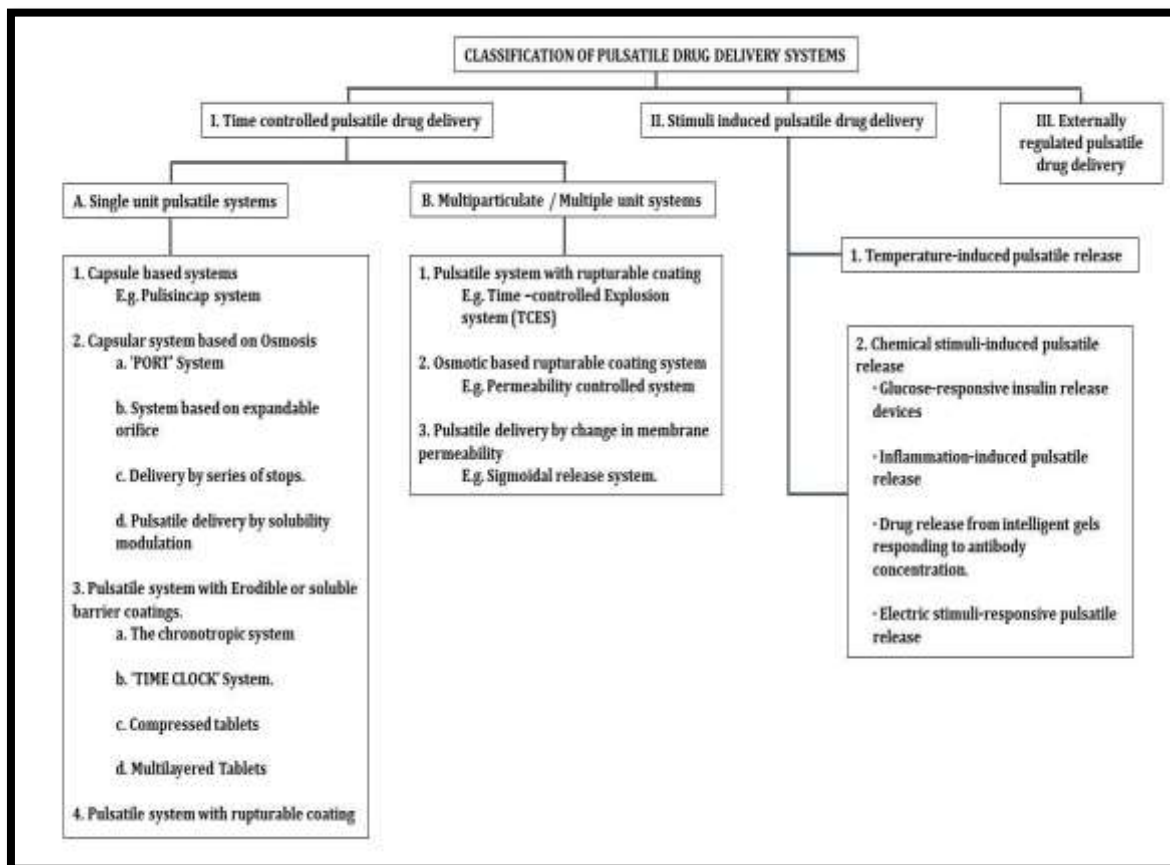


Fig no 3 classification of pulsatile drug delivery system [16]

A. Single unit pulsatile systems:

These are sub-classified as

1. Capsule-Based Systems
2. Osmotic Systems,
3. Delivery systems with soluble or erodible membranes, and
4. Delivery systems with rupturable coating

I. **Capsule based systems:** single-unit systems are mostly developed in capsule form. The lag time is controlled by a plug, which gets pushed away by swelling or erosion, and the drug is released as a “pulse” from the insoluble capsule body. Pulsincap® was developed by r. P. Scherer international corporation, michigan, us, and 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 . When this capsule came in contact with the dissolution fluid, it swelled; and after a lag time, the plug pushed itself outside the capsule and rapidly released the drug. Polymers used for designing of the hydro gel plug were various viscosity grades of hydroxyl propyl methyl cellulose, poly methyl methacrylates, poly vinyl acetate and

poly ethylene oxide. The length of the plug and its point of insertion into the capsule controlled the lag time. Pulsincap® was studied in human volunteers and was reported to be well tolerated⁵⁻⁷. A low-volume diagnostic test kit was marketed in 1997 under the trade name of ‘sprintsalmonella’ by oxoid ltd., basingstoke, u.k. steven et al. Developed a pulsincap® system with erodible compressed tablet⁸ . As the swelling hydrogel polymer plug replaced the erodible tablet.

II. **Systems based on osmosis:**

a. The Port® system was developed by Therapeutic system research laboratory Ann Arbor, Michigan, USA, and consists of a capsule coated with a semipermeable membrane. Inside the capsule was an insoluble plug consisting of osmotically active agent and the drug formulation¹³. When this capsule came in contact with the dissolution fluid, the semipermeable membrane allowed the entry of water, which caused the pressure to develop and the insoluble plug expelled after a lag time (fig. 3). Such a system was utilized to deliver methylphenidate used in the treatment of attention deficit

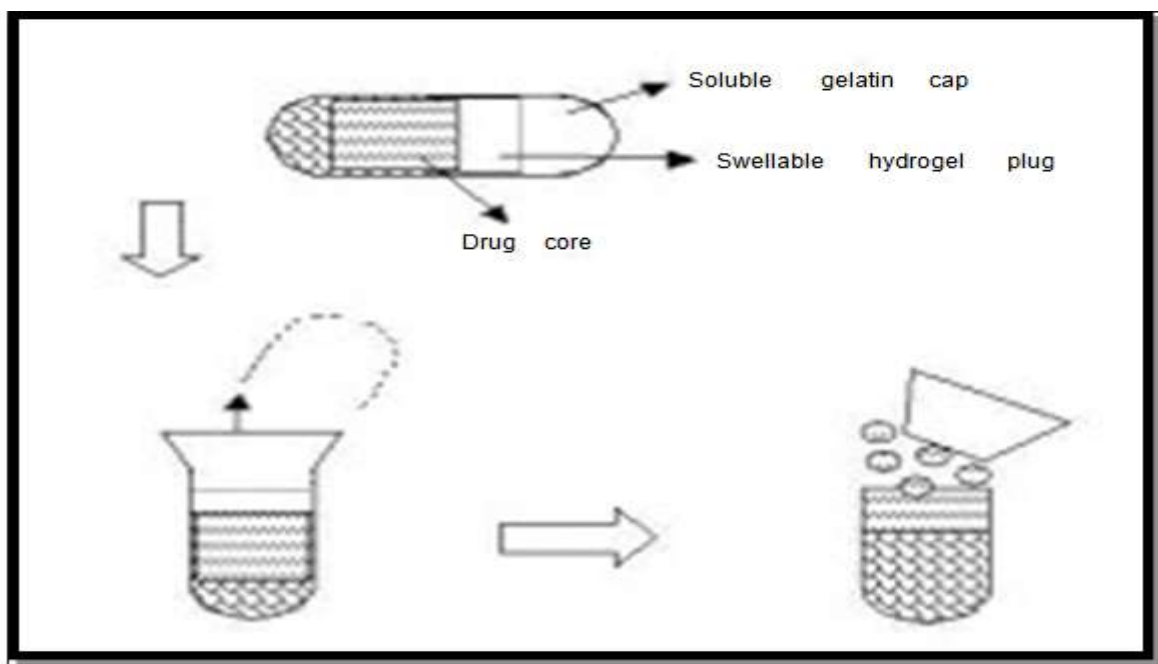


Fig. 4: Design of Pulsincap® system.

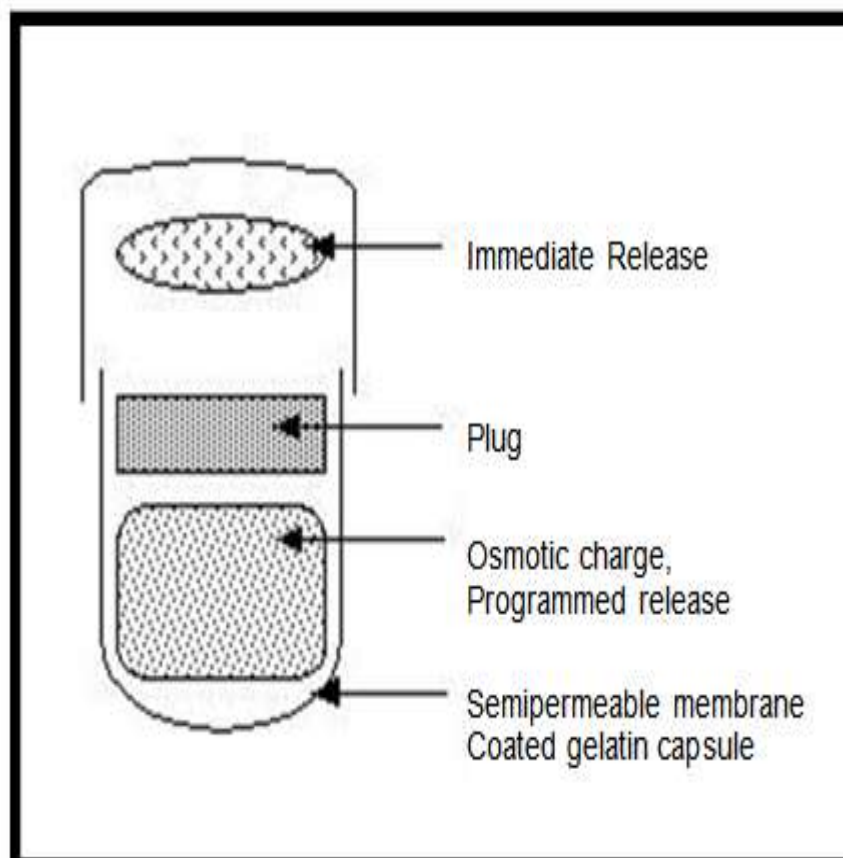


Fig. 5: Plan of Port[®] system.

Drug delivery system with eroding or soluble barrier coating:

These systems are based upon a drug reservoir surrounded with a soluble barrier layer that dissolves with time, and the drug releases at once after this lag time. Chronotropic[®] system consists of a core containing drug reservoir coated by a hydrophilic polymer HPMC. An additional enteric-coated film is given outside this layer to overcome intra-subject variability in gastric emptying rates¹⁸. The lag time and the onset of action are controlled by the thickness and the viscosity grade of HPMC.

The time clock system is a delivery device based on solid dosage form that is coated by an aqueous dispersion⁴¹. This coating is a hydrophobic-surfactant layer to which a water-soluble polymer is added to improve adhesion to the core. Once in contact with the dissolution fluid, the dispersion rehydrates and redisperses. The lag time could be controlled by varying the thickness of the film. After the lag time, i.e., the time required for rehydration, the core immediately releases the drug. This system has shown

reproducible results in vitro and in vivo. The effect of low calorie and high calorie meal on the lag time was studied using gamma scintigraphy⁴¹

III. Drug delivery system with rupturable layers/ membranes:

These systems are based upon a reservoir system coated with a rupturable membrane. The outer membrane ruptures due to the pressure developed by effervescent agents or swelling agents. Sungthongjeen et al. designed a pulsatile drug delivery system where the tablets of buflomedil HCl prepared by direct compression with varying amounts of spray-dried lactose and microcrystalline cellulose were coated with an inner swelling layer using croscarmellose sodium and an outer rupturable layer using ethyl cellulose. It was observed that by increasing the amount of ethyl cellulose coating, the lag time could be prolonged. Ethyl cellulose, being water insoluble, retarded the water uptake. Similar results were obtained with croscarmellose sodium. Increasing the amount of microcrystalline cellulose decreased the lag time substantially⁴¹.

Bussemer et al. worked on a pulsatile system with rupturable coating on drug present in hard gelatin capsules. These capsules were first coated with a swelling layer and then with an insoluble but waterpermeable outer coating. These coated capsules when immersed in the release media could take up the media at a constant rate up to a point when the outer coating would rupture

because of the pressure caused by the swelling layer. It could be concluded that by increasing the swelling layer, the lag time could be shortened. However, by increasing the outer coating, the lag time could be prolonged. It was also observed that addition of HPMC to the outer coating shortens the lag time^[4].

Diseases and needs of pdds

Table no. 1 . Diseases that require pulsatile drug delivery ^[1].

Disease	Chronological behavior	Drugs used
Peptic ulcer	Acid secretion is high in the afternoon and at night.	H ₂ blockers
Cancer	The blood flow to tumors is threefold greater during each daily activity phase of the circadian cycle than during the daily rest phase.	Vinca alkaloids, taxanes
Duodenal ulcer	Gastric acid secretion is highest at night, while gastric and small bowel motility and gastric emptying are all slower at night.	Proton pump inhibitors
Neurological disorders	The central pathophysiology of epilepsy and the behavioral classification of convulsive events.	Mao-b inhibitor
Hypercholesterolemia	Cholesterol synthesis is generally higher during night than day time.	Hmg coa reductase, inhibitors
Diabetes mellitus	Increase in the blood sugar level after meal.	Sulfonylurea, insulin
Arthritis	Level of pain increases at night.	Nsaids, glucocorticoids
Cardiovascular diseases	Bp is at its lowest during the sleep cycle and rises steeply during the early morning.	Nitroglycerin, calcium channel, blocker, ace inhibitors
Asthma	Precipitation of attacks during night or at early morning.	B ₂ agonist, antihistamines
Attention deficit syndrome	Increase in dopa level in afternoon.	Methylphenidate

Need of pdds

1. Their activity increases or decreases with time. A number of hormones like rennin, aldosteron, and cortisol show daily as well as timely fluctuations in their blood levels. Circadian effects are also observed in case of ph and acid secretion in stomach, gastric emptying, and gastro-intestinal blood transfusion.
2. Acid secretion, gastric emptying, cholesterol synthesis, and gastrointestinal blood transfusion may alter with circadian rhythm.
3. Chrono pharmacotherapy of diseases which shows circadian rhythms in their path physiology like bronchial asthma, myocardial infarction, angina pectoris, rheumatic disease, ulcer, and hypertension.

4. Lag time is essential for those drugs undergo acidic degradation (e.g. peptide drugs) that irritate the gastric mucosa or induce nausea and vomiting.
5. Targeting a drug to distal organs of gastro-intestinal tract (git) like the colon the drug release should be prevented in the upper two-third portion of the git.
6. Drugs undergoes extensive first pass metabolism that easily given by pulsatile drug delivery system ^[13]

Recent advances in the pulsatile drug delivery:

Nowadays pulsatile drug delivery systems are gaining importance in various disease conditions specifically in diabetes where dose is required at different time intervals. Among these

systems, multi-particulate systems (e.g. pellets) offer various advantages over single unit which include no risk of dose dumping, flexibility of blending units with different release patterns, as well as short and reproducible gastric residence time. Multiarticulate systems consists pellets of different release profile which can 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 achieve improved therapeutic efficacy. Gastroretentive drug delivery system is an approach to prolong gastric residence time, thereby targeting site specific drug release in upper gastrointestinal (gi) tract. Floating drug delivery system (fdds) and bio adhesive drug delivery are widely used techniques for gastro retention. Low density porous multiarticulate systems have been used by researchers for formulation of fdds. Sharma and Pawar developed multiarticulate floating pulsatile drug delivery system using porous calcium silicate and sodium alginate for time and site specific drug release of meloxicam. Various pulsatile technologies have been developed on the basis of methodologies as discussed previously (table-4).

A. Oros® technology: chronset™ is a proprietary oros® delivery system that reproducibly delivers a bolus drug dose in a time- or site-specific manner to the gastrointestinal tract. It is nothing but osmosis based system. The active pharmaceutical is kept in a reservoir surrounded by a semipermeable membrane laser drilled with a delivery orifice and formulated into a tablet. There are two layers in this tablet comprising of one drug layer and another osmotically active agent. Upon contact with gi fluid this osmotic agent changes its characteristic from non-dispensable to dispensable viscosity. As a result active pharmaceutical is pushed away through the channel due to pump effect of the osmotic agent. It is used generally for designing of extended release tablet.

B. Ceform®: it produces uniformly sized and shaped microspheres of pharmaceutical compounds. This approach is based on “melt spinning” which means subjecting solid feedstock (i.e. biodegradable polymer/ bioactive agent combinations) to a combination of temperature, thermal gradients, mechanical forces, flow and flow rates during processing. The microspheres

obtained are almost perfectly spherical, having a diameter that is typically of 150–180 mm, and allow for high drug content. The microspheres can be used in a wide variety of dosage forms including tablets, capsules, suspensions, effervescent tablets and sachets. The microspheres may be coated for controlled release with an enteric coating or may be combined into a fast/slow release combination^[16]

A. Diffucaps® technology: this technology is nothing but capsule based system containing one or more drug-containing particles (e.g. beads, pellets, granules etc.). Each bead shows pre-programmed rapid or sustained release profile with or without lag time. It has been already discussed in system with erodible, soluble or rupturable membrane section.^[16]

B. Contin® technology: here cellulose polymer and a nonpolar solid aliphatic alcohol constitute molecular coordination complexes between them. At first that polymer is solvated with a polar solvent. Alcohol may be optionally substituted with an aliphatic group. This alcohol is added to the solvated polymer preferably as a melt. After addition it forms the coordination complex having utility as a matrix in controlled release formulations since it has a uniform porosity which may be varied. It is also applicable for designing of controlled release tablets. This technology has sufficient control over drug release to the blood and reduces the chances of unwanted side effects.^[16]

B. Chronotopic® technology: it is also described in system with erodible, soluble or rupturable membrane system. It is basically drugcontaining core coated with an outer releasecontrolling layer. Both single and multiple unit dosage forms such as tablets and capsules or minitables and pellets have been employed as the inner drug formulation.

C. Egalet® technology: it is a delayed release form consisting of an impermeable shell with two lag plugs, enclosing a plug of active drug in the middle of the unit. After erosion of the inert plugs the drug is released. Time taken to erode the inert plugs determines the lag time. The shells are made of slowly biodegradable polymers (e.g. ethylcellulose) and plasticizers (such as cetostearyl alcohol), while the matrix of the plugs is a mixture

D. Codas® technology: chronotherapeutic oral drug absorption system (codas) technology is a multiparticular system designed for bedtime dosing. Here nonenteric coating is applied on drug loaded beads to delay the release of drug

up to 5 h. Here release controlling contains mixture of both water-soluble and water-insoluble polymers. When this dosage form comes in contact with GI fluid water-soluble polymer gets dissolved slowly and pores are formed on the coating layer. Drug diffuses through these resulting pores. Water-insoluble polymer acting as a barrier maintains the controlled release fashion like release of verapamil^[16]

E. timerx® technology: it is hydrogel based controlled release device. This technology can provide from zero order to chronotherapeutic release. It can provide different release kinetics by manipulating molecular interactions. The authors claimed that the “molecular engine” replaces the need for complex processing or novel excipients and allows desired drug release profiles to be “factory set” following a simple formulation development process. Basically, this technology combines primarily xanthan and locust bean gums mixed with dextrose. The physical interaction between these components works to form a strong, binding gel in the presence of water. Drug release is controlled by the rate of water penetration from the gastrointestinal tract into the timerx gum matrix, which expands to form a gel and subsequently releases the active drug substance^[16]

F. port® technology: the programmable oral release technologies (port) system is a uniquely coated, encapsulated system that can provide multiple programmed release of drug. It contains a polymeric core coated with a semipermeable, rate-controlling polymer. Poorly soluble drugs can be coated with solubilizing agents to ensure uniform controlled release from the dosage form. In capsule form had gelatin capsule is coated with a semipermeable, rate-controlling polymer. Active medicament mixed with osmotic agent is kept inside capsule shell. A water-insoluble plug is used to seal the capsule shell. Immediate release compartment can be added according to need^[16]

Advantages of pdds

1. These systems can be used for extended day time or night time activity.
2. They reduce the dose frequency, dose size and cost, which ultimately reduces side effects, thereby improving patient compliance.

3. Drug adapts to suit circadian rhythms of body functions or diseases.
4. Drug targeting to specific site like colon can be achieved.
5. They also protect mucosa from irritating drugs.
6. Drug loss by extensive first pass metabolism is prevented.
7. They provide constant drug levels at the site of action and prevent the peak-valley fluctuations^[11].

Disadvantages of pdds

1. Low drug loading capacity and incomplete release of drug.
2. Multiple manufacturing steps^[11]
3. Low drug loading capacity and incomplete release of drug.
4. Higher cost of production.
5. Large number of process variables.
6. Lack of manufacturing reproducibility and efficacy.
7. Batch manufacturing process.
8. Unpredictable ivivc.
9. Need of advanced technology^[13]

Applications of pulsative drug delivery system

- A. Treatment of diseases such as cardiac arrest during sleep, early morning asthma attacks and joint stiffness etc., where pathophysiology of disease is controlled by circadian rhythm of human body.
 - B. Drugs having high first pass metabolism can be easily given by pdds e.g. proteins and peptides.
 - C. Pdds can reduce the tolerance of drugs by decreasing exposure of drug in the body.
 - D. Drug targeting to distal part of GIT such as colon is possible by the use of pdds.
- E.** Drugs with short $t_{1/2}$ e.g. β -blockers.
- F.** Treatment of confined disorder where drugs should be delivered to the site of inflammation without any drug loss for maximum therapeutic benefits with minimum adverse effects e.g. inflammatory bowel disease.
- I.** Protection of drugs from the acidic environment of stomach.
- G.** Protection of mucus layer of the stomach from certain drugs e.g. peptide drugs^[19]

Limitations of pulsatile drug delivery system

pulsatile drug delivery systems have certain limitations, so in many cases these drug delivery systems fail, 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.^[12]

II. CONCLUSION:

Oral drug delivery is the largest, oldest, and most preferred route of drug delivery. Universally sustained and controlled-release products provide a desired therapeutic effect, but fail for diseases following biological rhythms. Circadian disorders such as asthma, osteoarthritis, cholesterol synthesis, etc., require chronopharmacotherapy. Pulsatile drug delivery can effectively crack this problem as it is modulated according to body's circadian clock giving release of drug after a specified lag time. During the last two decades, technologies to ensure time controlled pulsatile release of bioactive compounds have been developed.

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