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PULSATILE DRUG DELIVERY SYSTEM

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Abstract:

Pulsatile Drug Delivery systems are gaining a lot of interest. Pulse tile drug delivery system has attracted because of their multiple benefits over conventional dosage forms They deliver the drug at the right time and in the right amount thus they provide spatial and temporal delivery and increase patient compliance The pulse tile drug delivery systems which release the drug rapidly and completely after a lag time various systems like capsular system and osmotic systems, single and multiple unit systems based on the use of soluble and erodible polymer coating and use of rupturable membranes have been dealt with in the article (PDDS) is the most interesting time and site-specific system. These systems are beneficial for the drugs that have chronopharmacokinetic behavior.

Keywords: Pulsatile drug delivery system, PDDS, pulsatile drug release, circadian rhythm rupturable, osmotic erodible, single & multi-unit systems, Chrono pharmacokinetic drugs.

Introduction:

Pulsatile drug delivery systems, which release the drug rapidly and completely after a lag time thus provide spatial and temporal delivery and increase patient compliance This has generated increasing interest during recent years for several diseases and therapies Different types of pulse tile systems have been developed including eroding and rupturable systems have been developed. As the technology in the pharmaceutical industry has an advanced interest in drug delivery systems have grown during the past few years currently, the focus of pharmaceutical galenic research is focused on the creation of more effective drug delivery systems with existing chemicals instead of developing a new medicine due to difficulties that are posed by drug development and research process.

The drug delivery has typically intended for predicting the absorption from a straightforward chemical form either from the stomach or the injection site a control release pattern shows a difficult type of drug release fig 1 in which drug concentration is maintained in the therapeutic window for a prolonged period (Sustained release they're by ensuring a sustained release of action. The level of cortisol is higher in the morning unique drug delivery system that is quick and hours, with a reported steady drop in its release, and is reported to decline gradually completely after a lag time or a time when no drug is in the daytime.

Drug release pulse tile effect i.e, the release of drug as a Pulse after a lag time has to be designed in such a way that a complete and rapid drug release should follow lag (FIG2) Such systems are also time controlled as the drug release is independent of the environment. Though most delivery systems are designed for a constant release over a prolonged period. pulsatile delivery systems are characterized by a programmed drug release as constant blood levels of a drug not always be desirable (fig2)

Pulse tile systems are made such that the medication is accessible at the site of action at the right time in the right amount. These techniques are advantageous for drugs that have the first-pass effect, a medication used to treat ailments following Chrono pharmacological behavior drugs having specific absorption sites in GIT, targeting to; and cases where night-time dosing is required.

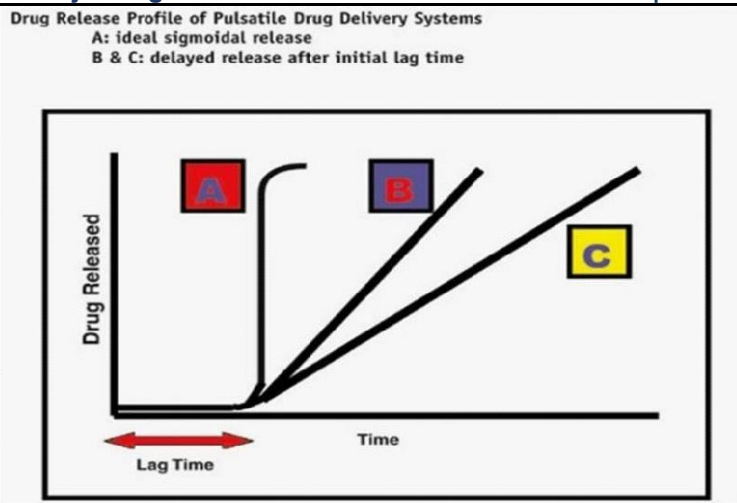


Fig 1: Drug release profile of pulsatile drug delivery systems

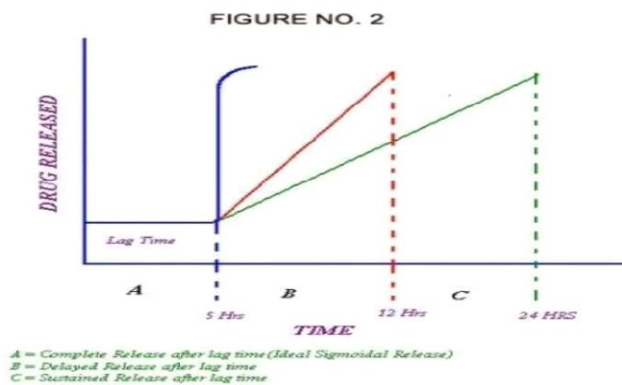


Fig 2: Drug release profile of pulsatile drug delivery systems

Chronopharmacokinetic: Recent studies have revealed that diseases have predictable cyclic rhythms and that the timing of medication regimens can improve outcomes in selected chronic conditions. Chrono pharmaceuticals consists of two words chronology and pharmaceuticals. chronobiology is the study of biology and its mechanisms .there are three types of mechanical rhythms in our body are

- Circadian
- Ultradian
- infradian

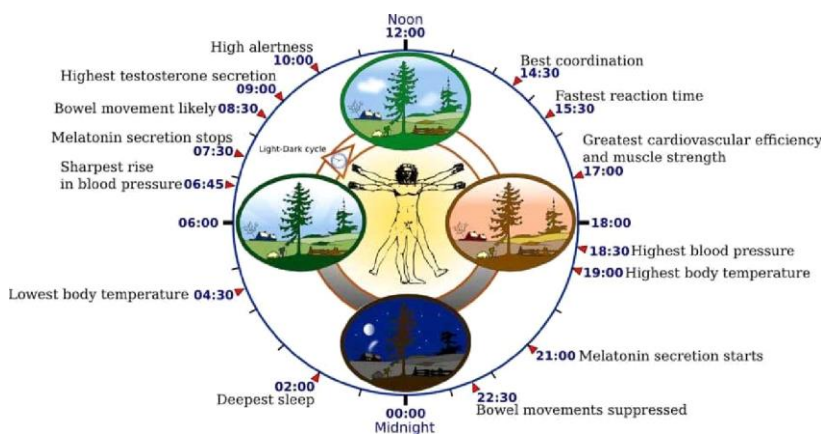


Fig-3: Represents cycle circadian rhythm

Pre-requisites of pulsatile drug delivery system:

Mainly most of the body functions follow the circadian rhythm means it increases or decreases with time. A no of hormones like renin, aldosterone, and cortisol show daily as well as timely variations in their blood vessels. These circadian effects are observed in the case of ph and acid secretion in the stomach, and gastric emptying (Goo1987) Ex: some medications such as salbutamol sulfate, cause gastrointestinal blood transmission.

2, Medicines that degrade in the acidic stomach environment and irritate the gastric mucosa Ex: Peptide drugs must be protected from the gastric environment. The drug release needs to stop to achieve the localized action at the distal organs of GIT like the colon of ulcerative colitis medications (like sulfasalazine) the drug release needs to be prevented in the upper two third portions of the GIT (Gazzaniga et al...,1994)

3, The drugs that undergo first-pass metabolism (B_BLOCKERS) are those with unique pharmacokinetic or pharmacodynamics that result in a reduced change in bioavailability, altered drug, and metabolite, and potential food drug interactions require delayed release of the drug to the extent possible.

All of these conditions demand an efficiently programmed drug delivery system to release the right amount of drug at the right time. This can be achieved by a pulse tile drug delivery system.

Methods of pulsatile drug delivery system

Currently available system: Pulsatile systems are time-controlled drug delivery systems in which the system controls the lag time independent of environmental factors like PH, enzymes, gastrointestinal motility, etc These time-controlled systems can be classified as single units eg. (tablet or capsules) or Multiple unit system(e.g...Pellets, beads)

SINGLE UNIT SYSTEM.

- Capsular system.
- Pulse tile system based on osmosis.
- A pulsatile system with an erodible or soluble barrier coating.
- A pulsatile system with rupturable coating.

MULTIPLE UNIT SYSTEMS

- Pulse tile system based on rupturable coating
- Osmotic based Rupturable coating systems
- Pulse tile system by a change in membrane permeability

Capsular system: There are Numerous single unit capsular pulse tile drug delivery methods available such systems typically have an insoluble capsule body that contains a plug and drug The plug could deteriorate bulge or soluble that it gets eliminated after a predetermined lag time. Th pulsincap system was developed by R.P.Scherer international corporation; Michigan, us, is an example of such a system that it is made up of a water-insoluble capsule body enclosing a drug reservoir. The body is closed at an open end with a swellable hydrogel plugupon contact with dissolution medium or gastrointestinal fluids the plug swells and after a lag time pushes itself out of the capsule. This leads to the drug releasing a pulse .controlling lag time involves altering the plug's dimensions and placements. The plug swells in response to digestive fluids and eventually forces itself out of the capsule This causes a pulse-like drug release controlling the lag time involves altering the plug's dimension and placements. Drugs that are not soluble in water can have a quick release by adding disintegrants or effervescent substances the substance for the plug is impermeable but also insoluble polymers that may expand (polymethacrylates) Polymers such as polymethaxylateswhich are impermeable but permeable and swellable and compressed polymers that are erodible (such as hydroxypropylmethylcellulose) congealed melted polymers eg: (saturated polyglycolide glycerides , glyceryl monooleate). There were no reports of gastrointestinal upset after using these formulations on healthy volunteers or animals. But there was a potential issue with overcoming varying gastric residence time by using an enteric coating to facilitate the disintegration of the system only in the small intestines' higher ph region of the small intestine.

Pulsatile system based on osmosis: This system was created to administer medications in liquid form while combining the advantages of high bioavailability and prolonged release. It consists of a gelatin capsule coated with a semipermeable membrane .along with the pharmacological formulation, the capsule also contained an osmotically active substance and an insoluble plug .after this the dissolving medium came into touch with the capsule, over the semipermeable barrier, water diffuses causing a rise in internal pressure that forces the plug following a predetermined delay. There is a delay thickness of the coating controls the system performed well. the experimental lag period in vivo and in vitro systems are correlated in people. Those systems were used to deliver the therapeutic drug methylphenidate for hyperactivity and attention deficit disorder (ADHD)in school-age children This system avoided a second daily dose that otherwise would have been administered by a nurse during school hours.

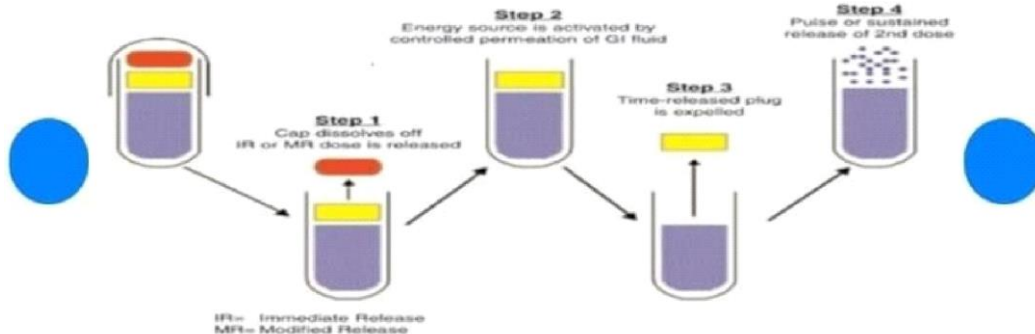


Fig-4: Represents a schematic diagram of the osmosis system (The port system)

Expandable orifice-based system: To deliver the drug in a liquid form. A capsular system based on osmotic pressure was created to distribute the medication in liquid form, in which the liquid medication is taken up by very permeable particles supported within a semipermeable capsule a delivery and an increasing osmotic layer barrier-covered orifice that releases the medication after the barrier layer through the delivery hole is eliminated. The provision of the osmotic infusion of the medication was what made it work .moisture from a physical environment is absorbed by the capsule. The wall of the capsule is comprised of an elastic substance and possesses a hole osmosis coating.

Delivery by series of stops: This system is made for implantable capsules and involves a series of stops in a compartmentalized capsule with a water-absorptive osmotic engine and a medication inside By a movable partition, the pulsatile delivery is achieved by a series of stops along the inner wall of the capsule. These stops obstruct the movement of the partition but are overcome in succession as the osmotic pressure rises above a threshold level. This system was used to deliver porcine somatotropin.

Pulsatile delivery by modulating solubility: For the pulsed delivery of a variety of medications such a system includes a solubility modulator. This system was specifically created .for the administration of salbutamol sulfate, an anti-asthmatic drug, salbutamol sulfate The pulsed delivery is made up of solubility of .salbutamol has a solubility of 321mg/ml in water and 16mg of/ml in a saturated solution of sodium chloride, while sodium chloride has a solubility of the drug is dependent on the modulator concentration.

Pulsatile system of adorable barrier coating: The majority of pulse tile drug delivery systems consist of barrier-coated reservoir devices. after a predetermined amount of time, this barrier erodes or disappears. The medicine is then quickly released after that. A lag period based on the coating layers thickness of the film this cart erodes or emulsifies in the aqueous environment, and the core is then available for dispersion. According to the study on human volunteers, the lag time was independent of the gastrointestinal residence time, and the redispersion of the hydrophobic films did not seem to be the presence of intestinal enzymes, and the ph of the gastrointestinal tract or the mechanical activity of the stomach The lag time lengthened as extending the coating thickness These systems are superior ideal for water-soluble medications. The main benefit of the simple equipment is required Nevertheless, such lipid-based systems might have a lot of video variation, There are few issues with erosion-controlled methods incorporating an early medication release when deep-seated disintegration The medication dissolves in liquid which steady diffusion through the barrier layers release when the barrier layer is present after the lag phase .when the barrier layer is not eroded or dissolve d completely, thereby retarding the drug release .multi-layered tablet: A Three layered tablet with two drug-containing layers and a drug-free layer between them produced a release pattern with two pulses barrier layers made of gullible polymeric. This tablet has three layers and was coated on three of the top and sides with impermeable ethyl cellulose. some of it wasn't coated. when in contact with a dissolution medium, the top layer containing the initial dosage was quickly freed from the uncoated surface. After a second pulse was acquired from the base layer. The HPMC gelling barrier layer deteriorated and dissolved When the second pulse emerged, it was governed by how quickly a substance dissolved or gels the protective layer. The reported gelling polymers consist of cellulose derivatives such as HPMC and methylcellulose. **pulsatile system based on rupturable coating:** These methods rely on the coatings disintegration for the release of the medication, as opposed to coating systems that swell or erode the strain necessary for the coating potential to rupture effervescent excipients which cause swelling osmotic pressure

, agents, or (Fig-4)an effervescent citric acid and sodium bicarbonate were combined included in a tablet core that has an ethyl coating cellulose. After carbon dioxide was ruptured, there is a pulsating release of the medication. The mechanical qualities may affect the release of a coating layer. The lag time increases with increasing coating thickness and increasing hardness of the core tablet .swellable agents are also referred to as super disintegrants utilized to create a capsule-based system with a swelling agent and polymer layer EX: cross carmellose, sodium starch glycolate, low substituted hydroxypropyl cellulose. The lag time was decreased by the addition of HPMC the device can be used to produce both solid and liquid medications. a previous setup that has a distribution of semi-permeable covering intended for medicines with a first-pass metabolism. The release pattern

resembled that which was attained following the administration of several immediate-release doses.

Advantage: manufactured easily

Disadvantage: in vivo variability which is present in GIT

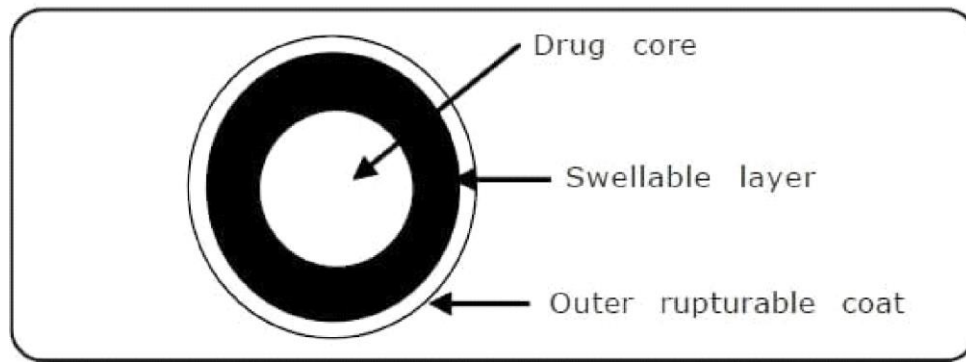


Fig-5: Represents schematic diagram of drug delivery with rupturable coating

Multi-unit system: Multiple-unit systems are those (eg; pellets beads) that offer various advantages over single-unit systems. These systems eliminate the possibility of dose dumping, offer flexibility in combining units with various release patterns, and short and repeatable gastric residence patterns, and short and regrettable gastric residence time. The inarticulate system's capacity for transporting drugs is lower since there is more excitement present. There are reservoir-type systems with either rupturable or permeability-altering coating and usually contained in the capsular body.

Pulsatile system based on rupturable coating: Time-controlled explosion system: This system used several particles and loads the medication by coating nonpareil sugar seeds then a layer that can inflate and a top that is insoluble layer allowed by swellable an insoluble top layer super disintegrants sodium starch with sodium carboxymethyl cellulose L hydroxypropyl cellulose and glycollate are utilized as swollen substances .utilised coating polymers include polyethylene glycol polyacrylic acid, and polyvinyl acetate are employed. A different option is an effervescent system. containing tartaric acid and sodium in combination Bicarbonate is another option upon entering the swellable layer expands when in contact with water, causing the film coat to rip followed by a rapid drug discharge The release stands alone from variables in the environment, including Ph Medication solubility. The lag time is influenced by lag time and quantities.

Osmotic-based rupturable system.

Permeability-controlled system:

The mechanism relies on a synergistic interaction between osmotic and swelling actions. This system includes a core that contains the medication, low bulk density fatty substances, both solid and liquid (Such as mineral oil), and an adhesive then, this core with cellulose acetate coating .when submerged in water permeates the core of aqueous media, displacing lipid

substances Following the removal of lipid material, until crucial stress is reached internal pressure increases .achieved, which causes the coating to rupture of coating. Another technique relies on a pill or capsule .comprised of several pellets of various sizes release strategy Each pellet contains a core that includes a water-soluble drug and a medicinal medication water permeable, water-insoluble polymer film placed on the osmotic agent a hydrophobic, insoluble in the water.

Another approach relies on a capsule or tablet made of several pellets of various sizes release strategy. Each pellet contains a core .that includes a water-soluble drug and medical medication water-permeable, water-insoluble polymer film placed on the osmotic agent a hydrophobic, insoluble in water permeability changing substance (Such as fatty acid, wax, fatty acid or its salt) is absorbed into the plastic film. Each formulation's film coating is unlike any other pellet coating in terms of dose in terms of water inflow and medication efflux rates. Water dissolves the osmotic agent, which results in the pellets swelling, controlling the rate of drug absorption diffusion. Each particle population's release impacts its medication content and gradually provides a series of pulses of drugs from a single dosage form. The coating thickness can be varied among the pellets. This system was used for the delivery of the antihypertensive drug diltiazem.

There are reports of people using osmotically active substances without edema The medication and sodium chloride makes up the pellet cores. These had a semipermeable cellulose acetate coating polymer. This polymer selectively allows the passage of water and is resistant to medication. A lag period rose as the coating thickness grew and more talc or a lipophilic plasticizer was included in the finish. The desired reaction was made possible by sodium chloride .rapid medication release. A lack of sodium chloride causes sustained release After the lag time due to the steady discharge attained. Core swelling to a lesser extent that led to the formation of tiny cracks a system with an osmotically active medication core sodium chloride, the active substance coated with an insoluble permeable membrane has also been proposed The coating materials reported include different types of poly (ACRYLATE METHACRYLATE)co polymers and magnesium stearate .which reduces water permeability of the membrane, thus allowing for use of thinner films. Thicker films are to be avoided as they do not rupture completely with the use of ethyl cellulose as a coating material. To achieve rupturing after a specific amount of time, it was able to alter the enteric polymers'

lag time by coating the material.

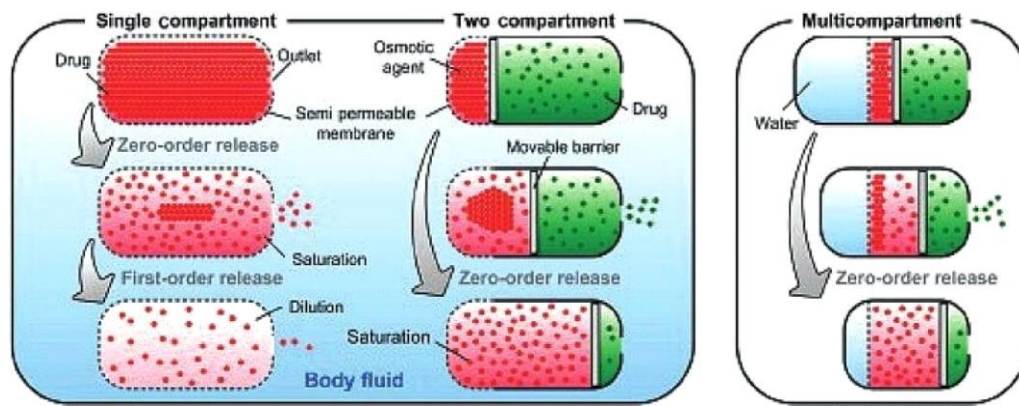


Fig:6 This picture represents the osmotic drug delivery system

Pulsatile system by changing membrane permeability:

The water absorption and permeability of quaternary ammonium-grouped acrylic polymers, such as Eudragit RS30D can be impacted by the existence of many oppositional ions in the medium. This ion exchange has been employed to create several delivery mechanisms. According to reports, Eudragit RS30D is a preferred polymer for this use. Typically, it includes quaternary ammonium which is a positively polarized group in the side chain of the polymer, which is always accompanied by the counter ions of negative hydrochloride. The hydrophilic nature of

the ammonium groups allow the alterations caused by polymer water interaction and its permeability, which makes it possible for water to pass fundamental activity that is managed. this house is attained a specified lag time.

The cores were made using sodium acetate and the model drug theophylline to cover these pellets, Eudragit RS 30D (10%40Weight) in four distinct layer thicknesses. AN association There was a correlation between film thickness and lag time. The outcome revealed a significant shift in medicine. the Eudragit films, permeability when even a little A small amount of sodium acetate was used in the center of the pellet. Following the delay, the interaction between the acetate and polymer increases between the acetate and polymer increases the permeability of the coating so significantly that the entire active dose is liberated within a few minutes., The lag time depended on the thickness of the coat, but the release of the drug was found to be independent of this thickness and dependent on the amount of salt present in this system.

Sigmoidal Release system: This consists of pellet cores containing drug and succinic acid coated with ammonium methacrylate co polymer. 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 the turn increases the permeability of the hydrate polymer film. In addition to succinic acid acetate acid, glutaric acid, tartaric acid, and malic acid you can use citric acid. The enhanced permeability can be attributed to the film being more hydrated, which raises the free volume. These outcomes are a coated delivery method with an acid-coating core. The in vitro lag time correlated well with invivo when tested in beagle dogs.

Marketed products: Many efforts are being made to create pulsatile release so that the medication can be administered by our body's circadian rhythms. Advanced pharmaceutical corporation, has created a daily pulse delivery mechanism. This system facilitates the delivery of amoxicillin antibiotics in continuous, routine pulses. The justification for creating such a system is that it has been reported that antibiotics are more effective against fast-growing bacteria. When an immediate-release antibiotic is administered, bacteria respond to it by going into a dormant stage, while the administration of the pulse tile system in such a case is more effective because the regular release of increased pulses doesn't allow the defense system of bacteria to go into a dormant stage.

The preclinical investigation has demonstrated that the pulsatile method of antibiotic delivery is more efficient .A bronchodilator is still another illustration. Theophylline is also known as uniphyl. Which was developed by Purdue pharmaceuticals products L P Stamford, Connecticut, and FDA approval in 1989. it is a daily formulation. whenever given in the morning, When blood levels are at their highest hours leading to better lung health and relief for the patient. For example in some situations varying plasma levels are needed during the day, Elan used a similar approach on Ritalin, a drug manufactured by NOVARTIS, which to obtain a pulsatile once-a-daily dose of methylphenidate form that takes the place of the twice-daily required.

Technology	Mechanism	API	Disease
Pulsys®	Timed-controlled system	Amoxicillin	Pharyngitis/transillitis
Uniphyl®	Externally regulated system	Theophylline	Asthma
Ritalina®	Osmatically regulated	methylphenidate	Attention Deficit Hyperactive Disorder (ADHD) - in children
Opana® ER	Timed-controlled system	Oxymorphone	Pain medicine
TheirForm®	Externally regulated system	Diclofenac	Inflammation

diseases require a pulsatile drug delivery system: A Complete comprehension of the physiology of the condition is before creating the pulsatile delivery medication system a condition in which rhythmic circadian key factor is how the body organized the drug's pharmacokinetics or pharmacodynamics within a day, drug use fluctuates. Table.1 lists several illnesses displaying such a temporal pattern behavior. In one such illness where a pulse tile breathing is a symptom using a drug delivery system may be beneficial. circadian alterations in typical lung function are observed, which reaches its lowest point early in the morning In cardiovascular disease case , many functions such as blood pressure, heart rate, stroke volume, and cardiac output, the cardiovascular system is subjected to circadian rhythms. capillary resistance and vascular reactivity are higher in the morning and decrease later in the day, reducing the inflammability of platelet aggregation is increased.

DISEASE	CHRONOLOGICAL BEHAVIOR	DRUGS USED
Peptic ulcer	Acid secretion is high in the afternoon and at night	H2 blockers
Asthma	Precipitation of attacks during night or at early morning hour	β 2agonist, Antihistaminic
Cardiovascular diseases	BP is at its lowest during the sleep cycle and rises steeply during the early morning awakening period	Nitroglycerin, Calcium channel blockers, ACE inhibitors etc.
Arthritis	Pain in the morning and more pain at night	NSAIDs, Glucocorticoids
Diabetes mellitus	Increase in the blood sugar level after meal	Sulfonylurea, Insulin, Biguanide
Attention	Increase in DOPA level in afternoon deficit syndrome	Methylphenidate
Hyper cholesterolemia	Cholesterol synthesis is generally higher during night than during day time	HMG CoA reductase inhibitors

Advantages of pulsatile drug delivery system:

- Extended daytime or nighttime activity.
- Reduced side effects and dosage frequency
- Improved patient compliance
- Drug loss is prevented by extensive first-pass metabolism (proteins or peptides)
- Predictable, reproducible, and short gastric residence time
- Protection of mucosa from irritating drugs.
- Drug adapts to suit circadian rhythms of body functions or diseases
- Avoid biological tolerance (e.g. Transdermal nitroglycerine).

Disadvantages of pulsatile drug delivery system:

- Higher cost of production.
- Low drug loading capacity and incomplete release of the drug.
- Batch manufacturing process.
- Low drug loading capacity and incomplete release of the drug.
- Trained or skilled personnel needed for manufacturing
- Lack of manufacturing reproducibility and efficiency
- Unpredictable IVIVC
- A large number of process variables

Recent advances in pulsatile drug delivery system: Pulsatile release formulations come in a variety of benefits compared to formulations for instant release. Less frequently used drugs with these formulas. Patient compliance and administration are both possible can be enhanced in line In the drug field delivery, more focus has recently been concentrated on the possibility of systems that can release medication following a configurable lag phase starting at the administration moment, starting in a pulsating manner mode. In the previous two decades technology to make certain that bioactive substances are released pulsatility and according to schedule.

- There has been advancement in achieving pulsatile techniques for administering drugs that are efficient for illnesses treated with nonconstant doses of medicine, like diabetes.
- However, there is a lot of work that needs to be done by carefully demonstrating pulsatile drug delivery of bioactive compounds, especially hormone problems as it is modulated according to the body's circadian clock gives the release of drugs by specific lag time.
- Recently in the last two decades, technologies that guarantee the pulsatile timing of bioactive substances have been designed for release.
- There has been a tremendous advancement toward developing a pulsatile medication delivery device that successfully that illnesses with variable dosage therapies There are several pulsatile technologies. analyzed and released to the market, which undoubtedly guarantees a successful and promising future.

Conclusion: It can be concluded that the pulsatile drug delivery systems offer a solution for the delivery of drugs exhibiting Chrono pharmacological behavior, extensive first-pass metabolism, the necessity of nighttime dosing, or absorption window in GiT. The most common method of administration used nowadays is the oral preferred pulsatile drug delivery method. Typically sustained and controlled-release medications deliver the intended therapeutic result but lack diseases that result from biological processes. Circadian disorders such as osteoarthritis, and asthma, require chronopharmacokinetics. A pulsatile drug delivery system can tackle this problem as it is modified according to the body's circadian clock giving the release of the drug after a specified lag time. Pulsatile drug delivery system that can cure illness with therapy involving irregular dosage. Therefore I conclude that the circadian rhythm of the body is an important concept for understanding the optimum need for the drug in the body. thus there is a constant need for new delivery systems that can provide increased benefits to patients. Many pulsatile technologies are studied, and some are already being used in the marketplace.

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