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A Review on Pulsatile Drug Delivery System

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ABSTRACT :-

Pulsatile drug delivery systems (PDDS) have gained significant attention in recent years due to their potential to optimize drug therapy by delivering drugs at specific times or in response to physiological rhythms. PDDS follows sigmoidal drug release where there is no drug release for some time period (lag time) and thereafter followed by a rapid and complete release. Lag time is independent on environmental factors like pH, enzymes, gastric motility etc., PDDS is useful for the diseases which follows circadian rhythms like asthma, hypertension, ulcers, etc. Pulsatile drug delivery systems (PDDS) can be categorized based on the mechanism of drug release: time-controlled systems release drugs based on a predetermined schedule, stimuli-induced PDDS release drugs in response to specific stimuli like pH or enzymes, and externally regulated systems depend on external factors like magnetism or ultrasound for drug release. Various systems like capsular systems, osmotic systems, single and multiple-unit systems based on the use of soluble or erodible polymer coating and use of rupturable membranes have been dealt with in the article. This review aims to provide a comprehensive and critical analysis of existing literature on pulsatile drug delivery systems (PDDS). Specifically, the review will: (i) Provide an overview of the current state of research on PDDS, including their applications, limitations, and potential for future development. (ii) Analyze the effectiveness of different types of PDDS for various diseases and conditions (iii) Provide recommendations for clinicians and researchers on the optimal use of PDDS in clinical practice

Keywords: Pulsatile drug delivery systems (PDDS), drug therapy optimization, sigmoidal drug release, lag time, circadian rhythms, clinical applications, limitations, future development, recommendations for clinicians, recommendations for researchers.

INTRODUCTION :-

In the pharmaceutical field, drug delivery systems have become more important in recent years. Pharmaceutical research is now focused on improving existing drug delivery methods instead of creating new drugs, as new drug development is challenging. Traditionally, drug delivery aimed to absorb a simple chemical from the gut or injection site. A newer goal is to deliver drugs at a constant rate, but living organisms don't work like this. They need varying amounts of a drug at different times to maximize benefits and minimize side effects. Efforts were made to design systems that release drugs at a constant rate until the early 1990s, which was successful for some drugs. However, this approach is not suitable for many drugs due to reasons like metabolic degradation and short half-life. For example, diabetes treatment often requires sustained-release drugs like sulfonylurea, but these can damage the pancreas. Drugs that lose effectiveness over time or have increased toxicity when levels are constant should not be given this way. Instead, drugs should be delivered in doses that provide the desired concentration at specific times. The concept of chronopharmaceutics is about designing drug delivery systems that release drugs in a way that matches the body's natural rhythms. Pulsatile Drug Delivery Systems (PDDS) release drugs in short bursts after a period of no release. Various techniques, like pH-dependent and time-dependent systems, are used to design PDDS. This review focuses on pulsatile drug delivery methods and upcoming technologies.

Various Modified Release Drug Products¹⁰

1. Extended Release: This formulation reduces the frequency of dosing by half compared to immediate release forms.
2. Controlled Release: This system allows for slow drug release over an extended period, although the release rate is not predetermined.
3. Sustained Release: This system delivers the drug at a predetermined rate over an extended period.
4. Delayed Release: This formulation releases discrete portions of the drug at times other than immediately after administration, although one portion may be released promptly after administration.
5. Targeted Release: These delivery systems deliver the drug at or near the intended site of action and may have extended release characteristics.
6. Repeated Action: This product is designed to release the first dose initially, followed by a second dose of the drug at a later time.

7. Prolonged Action: This formulation releases the drug slowly and provides a continuous supply of the drug over an extended period.

3.CHRONOBIOLOGY :-

Chronobiology is a branch of biology that studies the effects of time on living organisms and their biological rhythms. It focuses on the biological timing of physiological processes, including the circadian rhythms that govern the body's internal clock and regulate sleep-wake cycles, hormone production, and other bodily functions. Chronobiology also investigates how external factors such as light, temperature, and social cues can influence these rhythms and impact overall health and well-being. "Chrono" means time and biology means study or science of life

3.1 CHRONOPHARMACOLOGY:-

Chronopharmacology is a field of science that studies the effects of time on drug actions, including the timing of drug administration and the interactions between drugs and biological rhythms. It explores how the body's internal clock, known as the circadian rhythm, can affect the absorption, metabolism, distribution, and elimination of drugs, as well as their efficacy and side effects. Chronopharmacology aims to optimize drug therapy by considering the timing of drug administration in relation to the body's natural rhythms and biological processes.

3.2 CHRONO PHARMACOKINETICS: -

Chronopharmacokinetics studies how the body's rhythms affect drug absorption, distribution, metabolism, and elimination, aiming to optimize drug therapy.

3.3 CHRONOTHERAPY: -

Chronotherapy is the strategic timing of medication to enhance its effectiveness and reduce side effects, based on the body's natural rhythms.

3.4 CHRONOTHERAPEUTICS: -

Chronotherapeutics is the practice of administering medication at specific times to optimize its effectiveness and reduce side effects, taking into account the body's natural rhythms.

3.5 Biological rhythms⁵:-

Biological rhythms refer to the cyclical patterns or fluctuations in biological processes that occur in living organisms. These rhythms are influenced by internal biological clocks as well as external cues such as light, temperature, and social interactions. Biological rhythms can be daily (circadian), monthly (lunar), or annual (seasonal), and they regulate various physiological functions such as sleep-wake cycles, hormone secretion, and body temperature.

3.5.1 Types of biological rhythms^{5,14}:-

| Name of the Biological Rhythm | Oscillations durations time |
|-------------------------------|---|
| Circadian | Oscillations of a Day (Completed within a day or 24 hours) |
| Ultradian | The Oscillations are shorter durations type (>01cycle/24 hours) |

| | |
|------------------|---|
| Infradian | The Oscillations are longer durations type (<01 cycle/24 hours) |
| Seasonal | The oscillations are during short days of winter |

4. History and applications of chronotherapeutics: -

The first chronotherapy applied clinically was introduced in the 1960s, involving a schedule of alternate-day morning intake of conventional tablet corticosteroid medication. Since then, various other chronotherapies have been used in clinical medicine across the US, Europe, and Asia. These include evening theophylline systems for chronic obstructive pulmonary disease, conventional evening H₂ receptor antagonists for peptic ulcers, and conventional evening cholesterol medications for hyperlipidemia.

In the past 10-15 years, bedtime tablets and capsules for lowering blood pressure have been introduced. These release the drug in synchrony with the circadian behaviour of systolic blood pressure (SBP) and diastolic blood pressure (DBP) in primary hypertension (Smolensky et al., 2007).

5. Polymers used in pulsatile drug delivery systems: -

Pulsatile drug delivery systems, like those proposed by Langer et al., are critical for situations where continuous drug release is unsuitable, such as insulin delivery for diabetes. They use biodegradable PLGA copolymers with varying degradation rates as 'gatekeepers' to achieve pulsatile drug release. The system, based on a microchip made of poly (lactic acid), features reservoirs for drug solutions sealed with PLGA membranes. This approach can release different drugs from the same device, making it potentially useful for immunizations in developing countries. Moreover, because drugs are stored in reservoirs, this system is compatible with various drugs. The future of pulsatile drug delivery might involve systems that can actively modulate release based on demand, potentially tied to biosensors for real-time physiological feedback. For instance, insulin release could be linked to glucose sensor readings, enhancing blood glucose control in diabetes. Stimuli-responsive systems, such as those activated by ultrasonic energy or near-infrared light, offer more control but are more complex and costly. Nonetheless, the potential benefits of pulsatile dosing regimens and advances in materials science ensure continued interest in modulated drug delivery systems.

6. Classification of the pulsatile drug delivery system^{1,2,11,17}: -

A. Time controlled pulsatile release

I. Single unit system

i. Capsular system

ii. Port system

iii. Delivery by solubility modulation

iv. Delivery by reservoir systems with erodible or soluble barrier coatings II. Multi-particulate system

i. Pulsatile system based on rupturable coating ii. Time controlled expulsion system iii. Pulsatile delivery by change in membrane permeability iv. Sigmoidal release system

v. Low density floating multi particulate pulsatile systems

B. Stimuli induced:

I. Internal stimuli induced Pulsatile system

i. Temperature induced system ii. Chemical stimuli induced system iii. pH sensitive drug delivery system

II. External stimuli induced system

i. Electrically stimulates Pulsatile system ii. Magnetically stimulated Pulsatile system iii. Ultrasonically stimulated Pulsatile system

A. TIME CONTROLLED PULSATILE RELEASE: -

1. Single unit system: -

i. Capsular system: -

Various single-unit capsular pulsatile drug delivery systems have been developed. These systems typically consist of a water insoluble capsule body that contains the drug and a plug. The plug is designed to be removed after a specific amount of time, usually due to swelling, erosion, or dissolution.

The Pulsincap® system shown figure 1, developed by Scherer DDS, Ltd, is an example of such a system. It consists of a water-insoluble capsule body filled with a drug formulation. The open end of the capsule body is sealed with a swellable hydrogel plug. When the capsule comes into contact with a dissolution medium or gastrointestinal fluid, the plug swells, pushing itself out of the capsule after a predetermined lag time. This is followed by a rapid release of the drug.

The lag time before the plug is pushed out of the capsule can be controlled by adjusting the dimension and position of the plug. For drugs that are insoluble in water, a rapid release can be ensured by including effervescent agents or disintegrants in the formulation.

The plug material is typically made of insoluble but permeable and swellable polymers (poly ethylene glycol) erodible compressed polymers (Hydroxy propyl methyl cellulose), congealed melted polymers (e.g., saturated polyglycolated glycerides, glyceryl monooleate), or enzymatically controlled erodible polymers(pectin). These formulations have been well tolerated in animals and healthy volunteers, with no reports of gastrointestinal irritation.

One potential issue with these systems is the variable gastric residence time, which can be addressed by enteric coating the system to allow for dissolution only in the higher pH region of the small intestine.

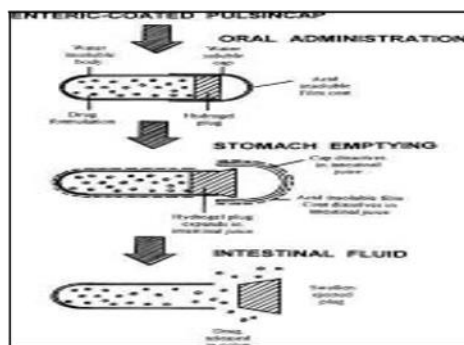


Figure-1

ii. Port system (programmed oral release technology): It is a capsular system based on osmosis. The Port® System, shown in Figure 2 and drug release mechanism is shown in figure 3. It's made of a gelatin capsule coated with a semi permeable layer (like cellulose acetate), a plug that doesn't dissolve in water, a substance that reacts with water to make pressure (osmotically active agent), and the drug itself. When the capsule comes in contact with aqueous medium, the water passes through the semipermeable layer and builds up pressure inside the capsule. After a while, the pressure gets so high that it pushes out the plug after lag time. The time it takes for the plug to be pushed out is controlled by how thick the semipermeable layer is. This system worked well in both invitro and invivo tests. It was made to deliver a drug called methylphenidate to kids with ADHD. This system means the kids don't need to take a second dose of the drug during school hours because the capsule can release the drug over time.

Further classification of the Port System is based on two main methods:

Expandable Delivery Orifices: This method is used for delivering drugs in liquid form. The drug reservoir develops osmotic pressure, which pushes the drug through delivery orifices. The lag time can be adjusted by changing the thickness of the barrier membrane.

Delivery by Series of Stops:

This method is used for implantable capsules. It involves a drug and a water-absorptive osmotic engine placed in compartments separated by movable partitions. Pulsatile drug delivery is achieved by a series of stops, with the number and frequency of stops, their longitudinal placements, and the length of the movable partition all playing a role in the delivery process.

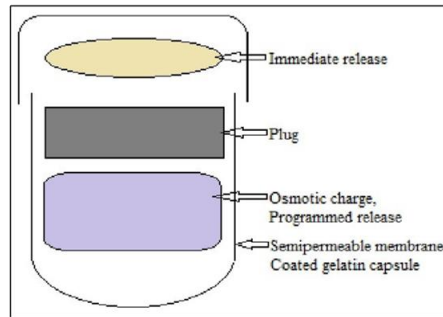


Figure-2

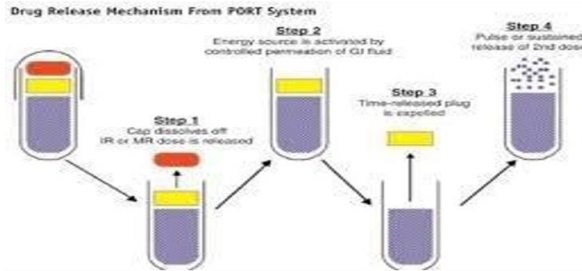


Figure-3

iii. Delivery by solubility modulation¹²: -

The Port System was designed to deliver liquid drugs, combining the benefits of extended release with high bioavailability. This liquid form is especially suitable for delivering drugs that don't dissolve easily, as well as large molecules like polypeptides and polysaccharides. Liquids are advantageous because they can dissolve, disperse, and protect these molecules from being broken down by enzymes.

The Liquid OROS Softcap™ (shown in figure 4), developed by Alza Corporation in the USA, includes layers for the liquid drug, an osmotic engine, a push layer, and a semi-permeable membrane coating. When the system is in contact with water, the water goes through the membrane and activates the osmotic layer. This layer expands, creating pressure inside the system, which pushes the liquid drug out through the delivery hole. The Liquid OROS hard cap™ (shown in figure 5) was made to hold more viscous drugs with higher drug-loading capacity. The time it takes for the drug to be released can be delayed from 1 to 10 hours, depending on how easily the drug goes through the membrane and how thick the barrier layer is. This technology has been used to create various OROS systems, like Procardia XL, Ditropan XL, and Concerti.

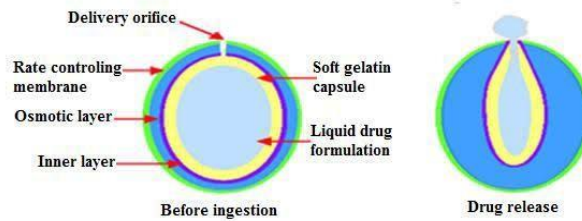


Figure -4

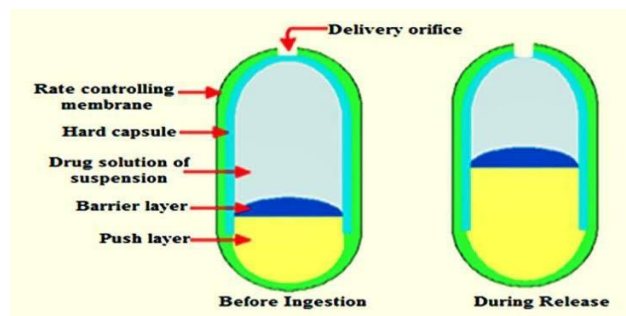


Figure -5

Delivery by reservoir systems with erodible or soluble barrier coatings:-

Many pulsatile drug delivery systems are reservoir devices coated with a barrier layer. This layer dissolves or erodes after a specific time, quickly releasing the drug. The lag time depends on the thickness of the coating.

The time clock system, shown in Figure 6, is made of a solid dosage form coated with lipidic barriers containing carnauba wax and beeswax, along with surfactants like polyoxyethylene sorbitan monooleate. This coating dissolves or emulsifies in water, which takes time based on the coating's thickness. Once the coating is gone, the core is released and ready to be dispersed. In a study with human volunteers, it was found that the lag time was not affected by how long the drug stayed in the stomach, and the re-dispersing of the hydrophobic film was not affected by stomach acids or enzymes. The lag time increased with the coating's thickness. This system is better for drugs that dissolve in water. The advantage of this system is that it's easy to make without needing special equipment. However, these lipid-based systems may have a lot of variation when used in the body (for example, the effects of food).

The Chronotropic system, also shown in Figure 6, is made of a drug-containing core coated with a hydrophilic, swellable hydroxypropyl methylcellulose (HPMC) layer. This HPMC layer causes a delay before the drug is released. By adding a gastric-resistant enteric film on the outside, the variability in how long the drug stays in the stomach can be reduced, and the drug can be released only in the colon. The delay in release is controlled by the thickness and type of HPMC used. The cores, containing antipyrine as a model drug, were made by compressing and coating them in a fluidized bed coater. The release curves in tests outside the body showed a delay before the drug was released, and the data from tests inside the body showed a delay before the drug was found in saliva. Both the tests outside and inside the body showed that the delay was related to the amount of HPMC used. This system can be used for both tablets and capsules.

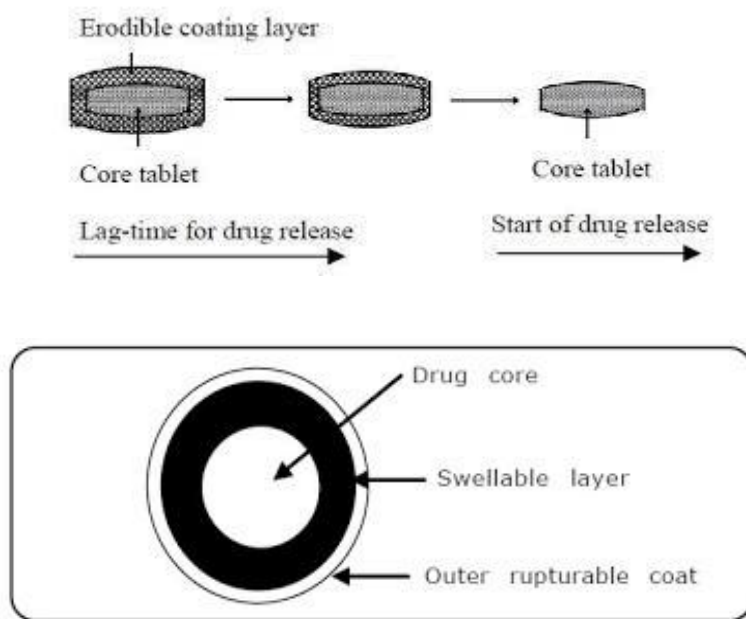


Fig.6 Schematic diagram of drug delivery with rupturable coating layer

2. Multi particulate system: -

Many systems, such as pellets and beads, have benefits over single-unit systems. These include no risk of dumping the whole dose at once, the ability to mix units with different release patterns, and a consistent and short time in the stomach. However, multiple systems can carry less drug because they have more excipients. These systems are usually reservoir types with coatings that can be rupturable or altered permeability coating.

Reservoir systems with rupturable polymeric coating⁶:

Many multiparticulate pulsatile delivery systems are reservoir devices with a rupturable polymeric layer. When water enters the system, the pressure inside builds up and the coating around the drug core breaks, releasing the drug. This pressure can be created by swelling agents, effervescent excipients that produce gas, or increased osmotic pressure. The time it takes for the coating to break depends on how easily water

can get through and how strong the coating is. Water-soluble drugs are mostly released by water getting through, and water-insoluble drugs are released when the drug dissolves.

Time-controlled explosion systems (TES) are a type of pulsatile delivery system where the drug is released by a unique mechanism that's not based on water getting through or the drug dissolving, but on the coating breaking. TES can be made as single or multiple unit dosage forms. In both cases, the core has the drug, an inert osmotic agent, and disintegrants. Each unit can be coated with a protective layer and then a semi-permeable layer, which controls how much water can get in. When water gets in, it creates osmotic pressure and the drug is released.

A four-layered time-controlled explosion system was made with the drug on an inner core (like polystyrene balls or sugar beads), followed by a layer that swells (like hydroxypropyl cellulose) and a top insoluble layer (like ethylcellulose). This system has the advantage of releasing the drug completely, no matter what the pH of the environment is or how well the drug dissolves.

ii Time controlled expulsion system: -

This system combines osmotic and swelling effects. The core has the drug, a low-density solid or liquid lipid material (like mineral oil), and disintegrants. The core is then coated with cellulose acetate. When the system is in contact with aqueous medium, the water goes into the core and displaces the lipid material. Once the lipid material is displaced, the pressure inside the core goes up until the coating breaks.

iii. Pulsatile delivery by change in membrane permeability: -

Acrylic polymers with quaternary ammonium groups can influence the permeability and water uptake depending on the counter ions in the medium. Some delivery systems use this to release slowly. One common polymer used for this is Eudragit RS 30D. It has positively charged quaternary ammonium groups and negatively charged hydrochloride ions.

These ammonium groups like to interact with water, so they change permeability. This lets water get into the drug inside in a controlled way. This is important to make sure the drug is released at the right time. In a study, the drug, theophylline and sodium acetate were put into pellets. These pellets were then coated with Eudragit RS30D at different thicknesses. The researchers saw that thicker coatings took longer to let the drug out. drugs but once the drug starts releasing, it releases quickly. This happened because the sodium acetate in the core of the pellets made the Eudragit RS30D more permeable after the lag time, so the drug releases faster

iv. Sigmoidal release system: -

This is a method that uses pellets made of a drug and succinic acid, covered 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 the succinic acid and the drug, which makes the polymer more permeable.

Other acids like acetic acid, glutaric acid, tartaric acid, malic acid, or citric acid can also be used. This increased permeability happens because the film gets more hydrated, which makes more space for the water. This method was tested in beagle dogs and the results matched what was expected from tests done outside the body.

v. Low density floating multi particulate pulsatile: Low-density multiparticulate pulsatile dosage forms stay in the stomach and are not affected by changes in pH, the local environment, or gastric emptying rate. These forms are useful for drugs that are absorbed in the stomach or need to be delivered there. In short, they are good for drugs that need to be released at a certain time and place in the stomach. A multiparticulate floating-pulsatile drug delivery system was made using porous calcium silicate (Florite RE) and sodium alginate. This system was used to release meloxicam in a specific way and at a specific time for treating rheumatoid arthritis.

STIMULI INDUCED

I. Internal stimuli induced Pulsatile system⁵:-

i. Temperature induced system: -

Temperature is a key factor in pulsatile drug delivery. When the temperature goes above the normal body temperature (37°C) due to pyrogens, it can affect drug release in various temperature-responsive drug delivery systems. These systems use temperature-sensitive polymers that respond to changes in temperature by swelling or shrinking. This swelling or shrinking affects the release of the drug. One example is thermosensitive polymeric micelles, which are used to carry drugs for cancer treatment. These micelles change their structure when the temperature changes, affecting how they release the drug. For example, when the temperature goes above a certain point, a layer forms on the surface of the micelles, stopping the release of the drug. This allows for precise control over when and how much of the drug is released.

ii. Chemical stimuli induced system: -

a insulin release device) Glucose-responsive s In diabetes, glucose levels in the body go up and down in a rhythmic pattern. To manage this, systems have been developed that can respond to changes in glucose levels. One such system uses a hydrogel that is sensitive to pH. Glucose oxidase, an enzyme, is trapped in the hydrogel. When glucose levels in the blood go up, glucose oxidase turns glucose into gluconic acid. This changes the pH of the system, causing the hydrogel to swell and release insulin. Insulin then lowers the blood glucose level, and as the level of gluconic acid decreases, the hydrogel stops swelling.

Some examples of pH-sensitive polymers that can be used are N,N dimethylaminoethyl methacrylate, chitosan, and polyol. A study by Obaidat and Park used a copolymer of acrylamide and allyl glucose. The glucose units in the copolymer were linked to concanavalin A, a protein. These hydrogels reacted to changes in glucose concentration by changing from a solution to a gel. Another study, by Okano, used copolymers with phenylboronic acid side chains. These copolymers formed reversible bonds with polyol compounds like glucose, leading to the formation of gels. These complexes would break apart when glucose was added, depending on its concentration.

b) Inflammation induced pulsatile release: -

When the body undergoes physical or chemical stress, like an injury or broken bone, it triggers an inflammatory response at the site of the injury. Cells like macrophages and polymorphonuclear cells play a role in healing during inflammation. During inflammation, hydroxy radicals (OH) are generated from these cells. Yui and their colleagues focused on these hydroxy radicals and designed drug delivery systems that responded to them and degraded in a controlled manner. They used hyaluronic acid (HA), which is broken down by hyaluronidase or free radicals. Under normal conditions, HA breaks down very slowly. However, when injected into inflammatory sites, it breaks down more rapidly due to the presence of hydroxy radicals. This allows for the treatment of inflammatory diseases like rheumatoid arthritis using anti-inflammatory drugs incorporated into HA gels as new implantable drug delivery systems.

C) Drug release from intelligent gels responding to antibody concentration: -

The body contains many bioactive compounds. New gels have been created that react to changes in the levels of these compounds, which affects how much they swell or shrink. Special attention was given to the formation of antigen-antibody complexes as the cross-linking units in the gel. This is because these interactions are very specific. By using antibodies that have been polymerized, and comparing them to naturally occurring antibodies, it's possible to create gels that swell or shrink in response to changes in the levels of specific bioactive compounds. This can change how drugs pass through the gel.

iii) pH-sensitive drug delivery systems: -

An effective way to design a time-release system is to use polymers that respond to changes in pH. These systems can be made as single units or as many small units with a predictable drug release profile. This system can work in different pH environments found in different parts of the gastrointestinal tract. This means that a system can be designed to target a specific part of the gastrointestinal tract and release the drug at a desired time. Examples of pH-sensitive polymers include copolymers of methacrylic acid (like various grades of Eudragit), phthalates, and carboxymethyl cellulose. These polymers are often used to coat drugs so they are protected from breaking down in the gastrointestinal tract and can be released in a specific part of the intestine, depending on the polymer's solubility at a specific pH and the location in the intestine. Many chronotherapeutic systems have been developed and marketed for treating asthma, angina pectoris, rheumatoid arthritis, cancer, diabetes, and ulcers. These systems use pH-sensitive polymers to release drugs at specific times in the body.

pH-dependent colon-targeted drug delivery systems:

The stomach has a pH of 2-3 (which increases after eating), the small intestine has a pH of 6.5-7, and the large intestine has a pH of 7-8. pH-sensitive polymers that contain carboxy groups, which make them insoluble at low pH values and soluble at higher pH values, are used to target drugs to the colon. Examples include Eudragit L (which is soluble at a pH greater than 6) and Eudragit S and FS (which are soluble at a pH greater than 7). These polymers are used to create drug delivery systems that release drugs specifically in the colon, where the pH is higher.

pH and time-dependent colon-targeted system:

Combining two or more polymers that are capable of delayed release based on the passage of time allows for targeted delivery in the terminal ileum and colon. For example, Eudragit L, S, or FS can facilitate transit from the stomach and small intestine. A second barrier of coating with a pH-independent polymer like Eudragit RS or ethyl cellulose provides delayed release for several hours. This approach allows for precise control over when and where the drug is released in the digestive system.

c) pH and bacterial enzymes-dependent colon-targeted drug delivery system: -

The CODES system combines polysaccharides that are degraded by enzymes and pH-dependent polymers. The outer coating consists of a polymer like Eudragit that dissolves after the dosage form has passed into the small intestine, exposing an undercoating layer of a different polymer like Eudragit E, which is soluble in acidic environments. This undercoating layer does not dissolve, but it allows for the release of lactulose into the environment adjacent to the tablet. These disaccharides are metabolized by bacteria, which lowers the pH and causes the Eudragit E to dissolve, releasing the drug. This system allows for targeted drug delivery to the colon, where the pH is lower and the bacteria are present.

II. External stimuli induced system¹⁹: -

Pulsatile drug delivery refers to a type of drug delivery that is both time-specific and site-specific. It can be achieved through two main methods: time-controlled or stimuli-mediated.

Time-controlled delivery means the drug is released at a specific time, while stimuli-mediated delivery means the drug is released in response to a certain stimulus, like a change in pH or the presence of an enzyme. Spatially controlled delivery involves the release of the drug in response to an internal stimulus, while temporally controlled delivery is in response to an external stimulus that can be controlled from outside the body. This allows for precise control over when and where the drug is released. Remote drug delivery systems can be designed to release the drug only when needed, providing an on-demand release profile

Magnetic pulsatile drug delivery systems:

Magnetic pulsatile drug delivery systems utilize magnetic microcarriers for targeted drug delivery, particularly in tumour sites, due to their effectiveness, low toxicity, and versatility. By embedding magnetic materials like magnetite, iron, nickel, or cobalt, these microcarriers can be activated by an external magnetic field to control drug release from a polymer matrix. This allows for precise control over the time, rate, and degree of drug absorption, as well as the ability to position the drug in specific locations or slow its contact with unwanted areas. Examples include magnetic steel beads embedded in a polymer matrix, which oscillate in response to a magnetic field, acting as a pump to expel drug molecules, and alginate spheres formulated for magnetically activated insulin delivery. Despite some challenges, magnetic microcarriers show promise for targeted and regulated drug delivery, with further research needed to establish their long-term safety and efficacy.

ii. Ultrasound pulsatile drug delivery systems:

Ultrasound has been used in medical imaging for decades. Recently, it has gained attention for its potential in combining with drugs for therapeutic purposes. This approach, called "sonodynamic therapy," has been explored in cancer treatment and diabetes management. In drug delivery, ultrasound waves can stimulate drug release from carriers and enhance vascular permeability. Pulsatile drug release can be achieved by breaking down the polymeric matrix. Ultrasound creates various effects in tissues, including pressure variation, acoustic fluid streaming, cavitation, and local hyperthermia, which help in drug release and absorption. Cavitation, for example, involves the expansion and contraction of microscopic bubbles, which release drugs and improve absorption. Acoustic streaming helps push particles into target tissues and destabilizes drug carriers. Hyperthermia converts ultrasound energy into thermal energy, releasing drugs from heat-sensitive vectors.

Studies have shown that ultrasound can increase drug release rates, as seen with polylactide matrices. In tumorized mouse models, ultrasound-induced microbubble explosions created micro cavitations in tumour cells, allowing anticancer drugs to enter more effectively. Polymeric nanoparticles have been used as drug carriers, and their release can be controlled with external ultrasound. Hydrogel microbeads with ultrasound-sensitive tungsten particles have been developed for on-demand drug release. Ultrasound-targeted microbubble destruction has been shown to improve exosome delivery in tissues like the heart, adipose tissue, and skeletal muscle.

However, the use of ultrasound in drug delivery raises safety concerns due to its interactions with tissues. Safety depends on parameters like frequency, intensity, duty cycle, and application time. Tissue type and environmental conditions also play a role.

iii. Electrically stimulated pulsatile drug delivery systems:

Electrically responsive drug delivery systems use implantable polymers or electronic devices to release drugs to specific locations at specific times. By applying external electrical fields, the voltage can be finely controlled to regulate drug release. This system has advantages, but high voltages can cause tissue damage and limit penetration depth. Biocompatible polyelectrolytes like carbomer, xanthan gum, and calcium alginate are commonly used in these systems.

For example, Kwon et al. studied the release of insulin from methacrylate hydrogels under electrical fields. They found that a small electric field increased local pH, which disrupted hydrogen bonds in the polymer and released the drug. Kim and Lee investigated the release of ionic drugs like cefazolin and theophylline from hydrogels under electrical fields.

Neumann et al. developed an electro-responsive drug delivery system using a bioresorbable nanocomposite film.

Electrochemical stimulation changed the local pH at the electrode surface, dissolving the pH-sensitive polymer carrier. In another study, sodium alginate and graphene oxide were crosslinked with Ca²⁺ to create an electro-responsive drug carrier. The electrical conductivity of graphene

oxide enabled the release of methotrexate under electrical stimulation. More recently, electro-responsive chitosan/magnetic nanoparticles composite microbeads were loaded with vancomycin. Additionally, a poly (2-ethylaniline) dextran-based hydrogel was formulated for transdermal drug delivery, releasing diclofenac in response to electrical stimuli.

iv. Light responsive pulsatile drug delivery systems:

Light-responsive drug delivery systems are attractive due to their non-invasive nature and ability to provide chronological control. They can be easily used and offer simplicity. Advances in this area include photochemically triggered release, photoisomerization, and photothermal release. Examples in clinical trials are thermosensitive liposomes and iron oxide nanoparticles.

Photochemically triggered release involves light irradiation causing covalent bond cleavage, leading to drug release. Moieties used in this method include o-nitrobenzyl, coumarin, and pyrene derivatives. Photoisomerization involves reversible conformational changes caused by light irradiation, often using azobenzenes. Photothermal activation uses a chromophore that converts light energy into thermal energy, releasing the drug. Materials used include gold nanoparticles and NiPAAm hydrogels.

Pearson et al. developed light-responsive glycopolymer micelles using azobenzene and β -galactose units to target melanoma cells. Wang et al. synthesized light-responsive coumarin-based dendrimers, which cross-linked upon irradiation at 365 nm and degraded at 254 nm, leading to enhanced anticancer activity. NIR light-responsive alginate hydrogels, when irradiated, showed rapid drug release, as demonstrated with doxorubicin. In another study, doxorubicin was incorporated into thermosensitive gold nanorods for light-responsive anticancer therapy, resulting in controlled drug release and efficient intracellular release upon NIR light irradiation.

V. Wireless controlled drug delivery systems: -

Wirelessly controlled drug delivery systems allow for on-demand and pulsatile drug delivery, making use of smart devices for easier and more user-friendly control. A safety processor system can enhance accuracy and safety by acting as a link between a mobile phone and a medical device, ensuring safe communication and examining command parameters. For instance, a system designed by Lee et al. involves a magnetically driven pump, an external control device, and a mobile application for precise and adjustable drug release. The mobile app sets dosing schedules and limits, can be controlled via Bluetooth for on-request administrations, and can prevent dosing errors or hypoglycaemia risks. The system also records administration history.

In a human trial, a microchip controlled wirelessly by a computer-based program was implanted to deliver a once-daily dose of an anti-osteoporosis drug to postmenopausal women. The drug release matched the expected pharmacokinetic profile of multiple injections without reducing drug efficiency. Another system, a wireless polymer conduction controller drug delivery system, consists of an electrochemical cell, a wireless remote controller device, and a wireless module that communicates with the controller. It is managed by a graphical user interface control program and effectively controls drug delivery.

Mechanism of drug release^{7,15}: -

The drug release mechanism from PDDS can occur through various processes:

1. **Diffusion:** When the PDDS comes in contact with aqueous fluids in the gastrointestinal tract (GIT), water penetrates into the particle's interior. This leads to drug dissolution, and the resulting drug solutions diffuse through the release coat to the exterior.
2. **Erosion:** Certain coatings can be engineered to gradually erode over time, thereby releasing the drug that is contained within the particle.
3. **Osmosis:** Under specific conditions, water can enter the particle, creating an osmotic pressure within its interior. This pressure forces the drug out of the particle and through the coating, releasing it into the external environment

Necessities for pulsatile drug delivery systems¹⁶: -

1. Fast drug input in Pulsatile Drug Delivery Systems is vital for drugs like beta blockers and salicylamide that undergo extensive first pass metabolism, ensuring better bioavailability.
2. Pulsatile Drug Delivery Systems help counteract biological tolerance often observed with continuous release drug plasma profiles.
3. Addressing specific chronopharmacological needs, like those related to circadian rhythms, can be achieved through Pulsatile Drug Delivery Systems, especially for diseases with time-specific symptom onset.
4. Local therapeutic needs, such as treating inflammatory bowel disease, benefit from Pulsatile Drug Delivery Systems by delivering compounds directly to the site of inflammation.
5. Pulsatile Drug Delivery Systems can help mitigate gastric irritation and chemical instability in gastric fluid, which may exacerbate with sustained release preparations.
6. For drugs with varying absorption rates in different gastrointestinal segments, Pulsatile Drug Delivery Systems can help ensure consistent and efficient drug absorption.

DISEASES THAT REQUIRES PULSATILE DRUG DELIVERY^{3,5,6}:-

A comprehensive understanding of the pathophysiology of a disease is essential before devising an appropriate drug delivery system. For diseases where the body's circadian rhythm plays a significant role, the pharmacokinetics and/or pharmacodynamics of drugs are not constant within a 24-hour period. It is shown well in figure -7

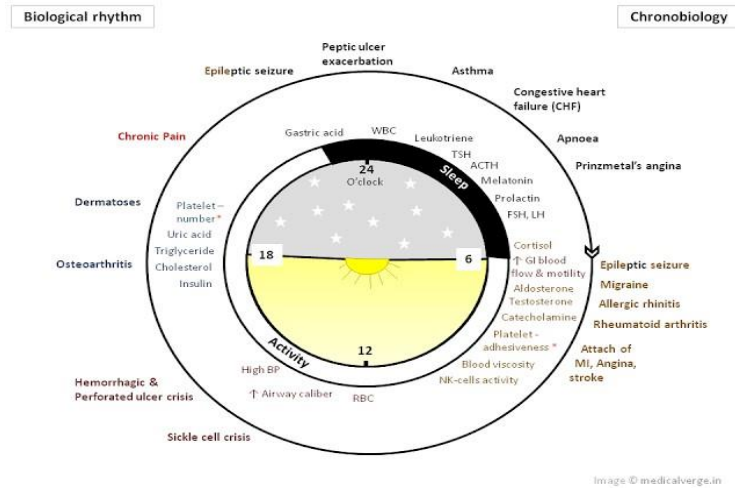


Figure -7

Chronopharmaceutical formulations are currently targeting diseases with sufficient scientific background to justify the use of pulsatile drug delivery systems (PDDS) over conventional drug administration methods. These diseases include asthma, arthritis, duodenal ulcer, cancer, diabetes, cardiovascular diseases such as hypertension and acute myocardial infarction, hypercholesterolemia, ulcers, and neurological disorders. The rationale for chronotherapy in these diseases will be briefly discussed below.

Table 1 : Circadian rhythm and the manifestation of clinical disease

| Disease | Chronological behaviour | Drugs |
|--------------|---|---------------------------|
| Asthma | Attacks tends to occur at the night or in the early morning | β2agonist, Antihistaminic |
| Peptic ulcer | Acid secretion is highest in the afternoon and at night. | H-2 blockers |

| | | |
|------------------------------|--|-------------------------------------|
| Duodenal ulcers | Gastric acid secretion is highest at night, while gastric and small bowel motility and gastric emptying are slower at night | H-2antagonists |
| Allergic rhinitis | Worse in the morning | Anti histamines |
| Rheumatoid arthritis | Pain is worse in the morning and at night. | NSAIDs and glucocorticoids |
| Osteoarthritis | Symptoms worse in the middle/late portion of the day | NSAID'S |
| Angina Pectoris | Chest pain and ECG changes more common in early morning | Antianginal drugs |
| Hypercholesterolemia | Cholesterol synthesis is generally higher during the night than daytime | HMG CoA reductase inhibitors |
| Myocardial infraction | Incidence higher in the early morning | Cardiovascular agents |

| | | |
|----------------------------|--|--|
| Strokes | Incidence higher in the morning | – |
| Sudden cardiac death | Incidence higher in the morning after awakening | – |
| Diabetes mellitus | Blood sugar levels rise after a meal. | Sulfonylureas, insulin, and biguanides |
| Attention Deficit Syndrome | Dopamine levels increase in the afternoon | Methylphenidate |
| Epilepsy | seizures may be more likely to happen at certain times of the day, depending on the individual's circadian rhythm. | Anti-epileptic drugs |

Table 2: Advanced technologies and marketed formulations of Pulsatile drug delivery systems^{5,6,8,10,14}:

| Technology | Mechanism | Proprietary name | API | Disease |
|------------------|--------------------------------------|------------------|-------------|-----------------|
| API modification | Physico chemical modification of API | Lipovas® | Simvastatin | Hyperlipidemi a |

| | | | | |
|-----------------------------|---|---------------------------|------------------------|-------------------------------|
| COER-24™ | Osmotically controlled onset and extended release | Covera-HS | Verapamil | Hypertension |
| CEFORM technology | Extended release | Cardizem@LA | Diltiazem HCl | Hypertension |
| CONTIN technology | Extended release | Uniphyll® | Theophylline | Asthma |
| CODAS™ | Extended release | Verelan@p M | Verapamil | Angina |
| DDR Technology | Dual drug release | Kapidex™ | Dexlansoprazole | Ulcers |
| Diffucaps™ | layering | InnoPran@X | Propranolol | Angina |
| Egalet® Technology | Delayed release with erosion method of drug delivery | Egalet® Technology | – | – |
| OROS | Extended | Covera- HS® | Verapamil | Hypertension |
| | release tablet | | HCl | |
| Geomatrix technology | Swelling/erosion | Coruno® | Molsidomine | Coronary heart disease |
| Pulsincap™ | Rupturable System | Pulsincap™ | Telmisartan | Angina pectoris |
| Ritalina | Osmotically regulated | – | Methylphenidate | ADHD |

| | | | | |
|-----------------------------------|---|------------------------|--------------------------|------------------------|
| TIMERx® | Erodible/ soluble barrier coating ER Tablets | OPANA® | Oxymorphone | Pain management |
| PULSYS™ | Multiparticulate system | Moxatag™ Tablet | Amoxicillin | Infection |
| PROCARDIA XL® | Sustained release | Procardia XL | Nifedipine | Hypertension |
| Three dimensional printing | Externally regulated system | Their Form | Diclofenac sodium | Inflammation |

10. Advantages and disadvantages of pulsatile drug delivery systems ^{2,4,9,18}

10.1 Advantages of Pulsatile Drug Delivery Systems (PDDS):

1. Predictable, reproducible, and short gastric residence time
2. Less inter- and intra-subject variability
3. Improved bioavailability
4. Reduced adverse effects and improved tolerability
5. Limited risk of local irritation
6. No risk of dose dumping
7. Flexibility in design
8. Improved stability
9. Improved patient comfort and compliance
10. Achieving a unique release pattern
11. Extending patent protection and globalizing products
12. Overcoming competition
13. Allowing for multiple dosing in a single dosage form
14. Enabling local treatment of diseases
15. Reducing dose frequency and risk of dose dumping, dose cost, dose size, and ultimately side effects
16. Decreasing drug interactions due to lower cytochrome P450 isoenzymes
17. Enabling the delivery of poorly bioavailable drugs that may be destroyed in the GI Tract
18. Decreasing food effect when the drug is taken with food
19. Not being affected by changes in GI tract pH, lumen viscosity, and agitation rate
20. Being applicable to different solid dosage forms, such as microspheres, granules, tablets, pellets, and capsules.

10.2 Disadvantages: -

1. Reproducibility and Efficacy Challenges in Manufacturing: The presence of numerous process variables and multiple formulation steps leads to a lack of manufacturing reproducibility and efficacy.
2. Cost of Production: The production of Pulsatile Drug Delivery Systems (PDDS) is associated with higher costs, primarily due to the need for advanced technology and trained or skilled personnel.
3. Advanced Technology: The manufacturing of PDDS requires advanced technological infrastructure and processes.

4. Skilled Personnel: The complex nature of PDDS manufacturing necessitates the involvement of trained and skilled personnel.

Current and Future scope^{4,9,11,13}: -

Nowadays, drug delivery systems are increasingly focused on the potential for timed release, or pulsatile delivery, which can release or deliver a drug after a specific, modified lag time. This approach reduces the frequency of doses and eliminates the risk of dose dumping. The pulsatile drug delivery system is seen as both a current and future method for treating certain diseases. It's considered more promising compared to zero or first-order drug delivery systems. The pulsatile release of a drug can be achieved and modified by using different coatings of the polymer and by altering the thickness of the coating on the drug.

The future of chronotherapeutics, particularly the future of delivering drugs in a pulsatile manner, appears promising for certain disease states, as pulsatile release offers several advantages over traditional zero or first-order drug delivery mechanisms. Pulsatile drug delivery systems can be either time-controlled or site-specific, with single or multiple units. At present, pulsatile release, whether site-specific or time-specific, is often achieved by employing different polymers in coating layers or by varying the thickness of the coating.

Conclusion: -

Traditionally drugs are given orally as they provide patients compliance and easy administration. The sustained and controlled release showed great success in drug delivery but failed to deliver drugs to treat diseases like asthma, hypertension, ulcers, etc., that follows circadian rhythms for which PDDS is very beneficial and increase the effectiveness of the medication, while decreasing the side effects and providing target based drug delivery. Numerous pulsatile technologies have been researched, and several are already in use in the market. Number of patents are filed by various companies recently. Still research is going on for developing PDDS. In future PDDS would be promising.

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