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A REVIEW ON PULSATILE DRUG DELIVERY SYSTEMS

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ABSTRACT

Pulsatile Drug Delivery Systems (PDDS) are innovative, time-controlled systems that manage drug release independently of external factors like pH, enzymes, and gastrointestinal motility.

Traditionally, drugs are released either immediately or over an extended period. However, pulsatile release systems have garnered significant interest recently, as they align with the body's circadian rhythms – where "circa" means "day" and "dian" means "night" in Latin. These systems are designed to release medication rapidly after a defined lag time, offering potential advantages for various therapies.

PDDS show promise for treating conditions such as asthma, peptic ulcers, cardiovascular diseases, arthritis, attention deficit hyperactivity disorder in children, and hypercholesterolemia. By synchronizing drug delivery with the body's internal clock, these systems ensure that medications are administered at optimal times, which can enhance therapeutic outcomes for chronic conditions like arthritis, asthma, and hypertension. The goal is to achieve complete and rapid drug release post-lag time, thus providing patients with timely and effective treatment.

1. INTRODUCTION

Oral drug delivery is the largest segment of the total drug delivery market and is the most preferred route for administering medications. Oral controlled-release systems typically maintain drug concentration within the therapeutic window over an extended period, ensuring sustained therapeutic effects. However, certain conditions require a different release pattern, specifically one that allows for drug release after a lag time. This leads to the need for pulsatile drug delivery systems (PDDS) Pulsatile systems are gaining attention because they release the drug completely after a defined lag time. Pulsatile drug delivery is characterized by time- and site-specific release, which enhances both spatial and temporal drug delivery, ultimately improving patient compliance. This type of delivery involves a rapid and transient release of a specific amount of the drug following a predetermined period without release.

Humans have endogenous circadian rhythms regulated by the body's master clock, the suprachiasmatic nucleus. Chronopharmacotherapy for diseases such as bronchial asthma, myocardial infarction, angina pectoris, rheumatic diseases, ulcers, and hypertension—conditions that exhibit circadian rhythms—requires pulsatile drug delivery systems. These systems enable rapid and complete drug release as a pulse after the lag time.

Additionally, many physiological functions, like hormone secretion (including FSH, LH, LHRH, estrogen, and progesterone), stomach acid secretion, gastric emptying, and gastrointestinal blood flow, also follow circadian rhythms and necessitate pulsatile release. Drugs that induce biological tolerance benefit from a delivery system that prevents their continuous presence in the body, as this can diminish their therapeutic effect. A lag time is crucial for drugs that may degrade in the acidic environment of the stomach (such as peptide drugs) or that may irritate the gastric mucosa and cause nausea.

Targeting drugs to distal areas of the gastrointestinal tract, like the colon, requires that release is delayed in the earlier sections of the gastrointestinal tract. Drugs that undergo first-pass metabolism, leading to reduced bioavailability and altered drug levels, also benefit from delayed release. All these factors should be considered when designing a delivery system that exhibits pulsatile release characteristics, ensuring the drug is released in a controlled manner at the appropriate site.

2. DEFINITION

The pulsatile drug delivery system is characterized by the quick and temporary release of a specific amount of drug molecules after a predetermined off-release period, known as lag time.

3. ADVANTAGES

- The pulsatile drug delivery system minimizes side effects.
- It effectively maintains the frequency of dosages.
- This technology allows for a reduction in dosage size.
- Patient adherence improves due to lower doses.
- It offers targeted action specifically for the colon.
- Drug loss is minimized due to reduced first-pass metabolism.

4. DISADVANTAGES

- Manufacturing consistency and effectiveness are low.
- There are numerous process variables.
- The formulation requires multiple steps.
- It necessitates advanced technology.

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5. DISEASES REQUIRED PDDS

Tablet No.1

Diseases	Chronological Behavior	Drug used
Arthropathy	Stress level arising during night.	Glucocorticoids, Painrelivers
Mellitus glycaemia	Blood glucose increase upon meal	Sulfonyl urea, Glucose
Hypercholesteremia	The synthesis of cholesterols generally high at night than during the day	Receptors of HMG CoA pyruvate Dehydrogenase
Physical impairment	The basic epilepsy Neurobiology of the infection and the identification for convulsive episode in behavior	MAO-Inhibitor
Ulcerative duodenal	Night times, whereas abdomen or intense cell proliferation or intense clearing are mostly slow at night.	Proton pump inhibitors
Asthma	Attack temperatures during night time or in the early morning	Antagonist of B2 Allergy medicines
Attention deficit Syndrome	Increase in DOPA level in afternoon	Methylphenidate
Ulcerative peptic	In the afternoon and night, acid secretions is strong.	H2 blocker
Back and heart disease	During the sleep cycle Bp is at its lowest and in the morning rises steeply	Sodium azide, receiver of iron channels, agonists of ACE
Cancer	During each daily phase, the blood flow to the tumors is three times greater during the phase of daily	Cannabinoid compound of Vinca, texanes

6. TIME-CONTROLLED PULSATILE RELEASE SYSTEMS

6.1 Stimuli-Induced Pulsatile Release System

Stimuli-based drug delivery systems release drugs in response to biological environmental changes. The release occurs through alterations in gels or micelles, which can swell, erode depending on the stimulus, such as temperature or chemical factors. Key mechanisms for drug release include:

1. Ejection: Drug is expelled as the fluid phase separates from the gel.
2. Diffusion: Drug moves along a concentration gradient.
3. Electrophoresis: Charged drugs migrate towards an oppositely charged electrode.
4. Erosion: Drug is liberated as the gel or micelle erodes.

There's significant interest in developing systems sensitive to specific enzymes or proteins, making them adaptable and excellent candidates for targeted drug delivery. These systems can be further classified based on their specific stimuli responses.

6.2 Thermoresponsive Pulsatile Release

Thermosensitive hydrogels are a type of polymer network that responds to temperature changes by undergoing reversible volume changes. These gels, which can be made from biological, synthetic, or semi-synthetic polymers, are being explored as drug delivery systems due to their ability to release drugs in response to temperature stimuli. The shrinking behavior of these gels occurs at a transition temperature related to the lower critical solution temperature (LCST) of the polymer used. Commonly, temperature-sensitive polymers contain hydrophobic groups such as methyl, ethyl, and propyl. One of the most widely studied thermosensitive polymers is poly(N-isopropyl acrylamide) (PNIPAm), which exhibits distinct swelling below 32°C and shrinking above this temperature.

Research by Krezanoskietal. introduced a reversed thermal gelation (RTG) system using polyol polymers like Pluronic®, which demonstrate low viscosity at room temperature and significantly increase in viscosity with rising temperatures. Additionally, Yuk et al. developed a temperature-sensitive drug delivery system combining poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) triblock copolymer (F-68) with polyvinyl alcohol (PVA). This system achieved a pulsatile release of acetaminophen due to temperature fluctuations between 35°C and 40°C.

6.3 Chemical Stimuli-Induced Pulsatile Release

The development of stimuli-sensitive delivery systems has gained significant attention for their ability to release therapeutic agents in response to biological factors like

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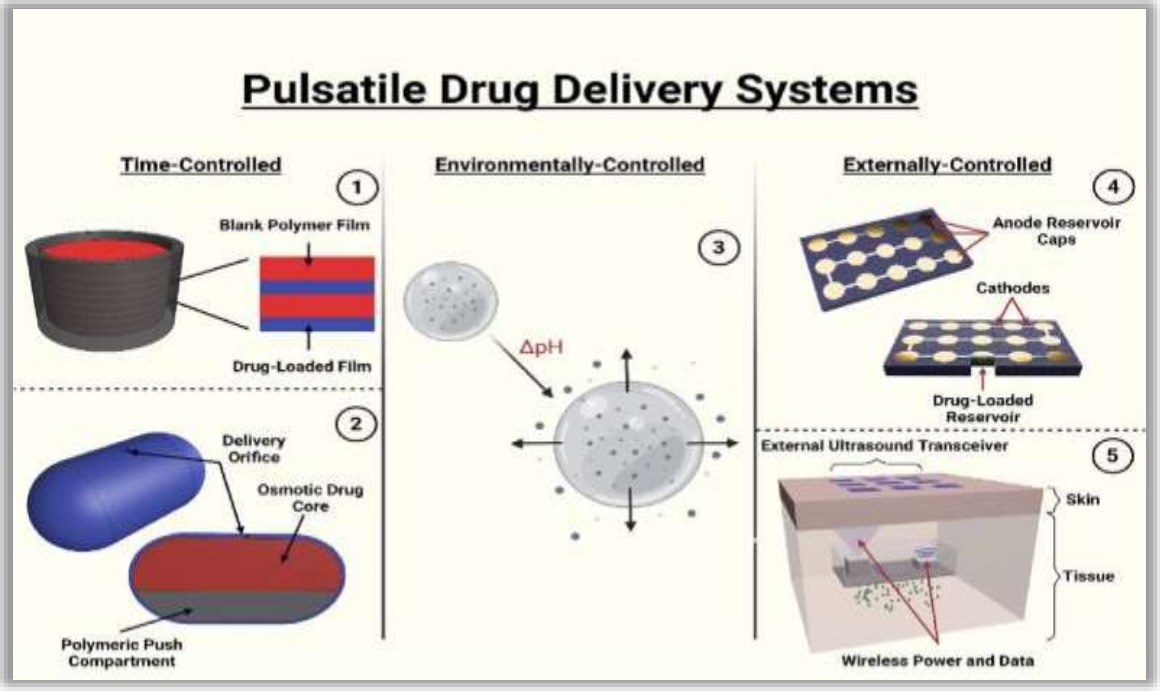
enzymes, pH, or other chemical stimuli. A notable application is the creation of systems that automatically release insulin when blood glucose levels rise Kazunori et al. developed a gel made of PNIPAAm combined with phenylboronic acid moieties, which displayed significant swelling changes in the presence of glucose. This glyco-sensitive gel shows promise for self-regulated drug delivery and other applications, including actuators and separation systems.

Another approach involves pH-dependent systems that utilize the oxidation of glucose to gluconic acid, a reaction catalyzed by glucose oxidase. This reaction can lower the pH to around 5.8 in glucose-rich environments, like post-meal blood. In this context, a dual membrane system was created: the first membrane, a glucose-sensing membrane, immobilized glucose oxidase within cross-linked polyacrylamide. The second membrane acted as a barrier between the insulin reservoir and the sensing membrane, composed of N,N-diethylaminoethyl methacrylate and 2-hydroxypropyl methacrylate (DEA-HPMA).

Fig No.1



7 EXTERNALLY REGULATED PULSATILE RELEASE SYSTEM

7.1 Electro Responsive Pulsatile Release

Electric fields serve as effective external stimuli for drug delivery systems, offering precise control over parameters such as current magnitude, pulse duration, and intervals. Electrically responsive delivery systems are typically made from polyelectrolytes, allowing them to respond to both pH and electric stimuli. When subjected to an electric field, these electroresponsive hydrogels can be swell, or erode. For instance, poly (2-acrylamide-2-methylpropanesulfonic acid-co-butyl methacrylate) (P(AMPS-co-BMA)) hydrogels have been utilized for electric stimuli-induced drug delivery. Kwon et al. explored these hydrogels, highlighting several mechanisms for drug release:

1. Drug expulsion as the gel's fluid phase syneresis occurs.
2. Drug diffusion driven by concentration gradients.
3. Electrophoresis, where charged drugs migrate toward oppositely charged electrodes.
4. Drug release due to gel erosion in response to varying electric field parameters.

Overall, the dual responsiveness of t4hese systems enhances their potential for targeted and controlled drug delivery.

7.2Ultrasonically Stimulated

Ultrasound is commonly employed to enhance drug permeation across biological barriers, such as skin, lungs, intestinal walls, and blood vessels. Numerous studies have highlighted its effectiveness in controlled drug delivery. For example, Kost and colleagues investigated ultrasound-enhanced polymers, while Miyazaki et al. demonstrated that ultrasound could achieve up to a 27-fold increase in the release of 5-fluorouracil from an ethylene and vinyl acetate (EVAc) matrix. They found that increasing the ultrasound intensity directly correlated with the amount of 5-fluorouracil released, showcasing the potential of ultrasound as a tool for improving drug delivery efficiency.

7.3 Magnetically Induced Pulsatile Release

The use of oscillating magnetic fields to regulate drug delivery from polymer matrices was one of the earliest methods explored for creating externally controlled drug delivery systems. Magnetic carriers, which can incorporate materials like magnetite, iron, nickel, or cobalt, respond to external magnetic fields. For biomedical applications, it's crucial that

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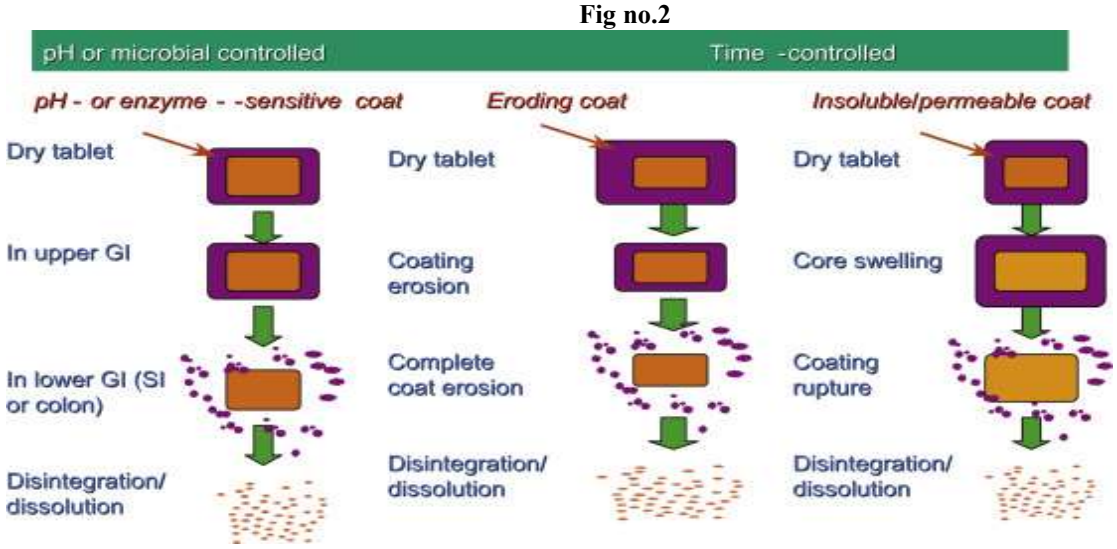
these magnetic carriers are water-based, biocompatible, non-toxic, and non-immunogenic.

The underlying mechanism involves using magnetic attraction to slow down the movement of orally administered drugs in the gastrointestinal tract. This is achieved by incorporating magnetic components into capsules or tablets. By applying an external magnet, the speed of travel through the stomach and intestines can be reduced at specific locations, thereby altering the timing and extent of drug absorption in these areas. This approach offers potential for more controlled and targeted drug delivery.

Fig no.2



8. MARKETED TECHNOLOGIES OF PULSATILE DRUG DELIVERY

8.1 Pulsincap Technology

Pulsincap, developed by R.R. Scherer International Corporation, is a drug delivery system consisting of a non-dissolving capsule with a hydrogel plug sealed by a water-soluble cap. The capsule is coated with an enteric polymer to prevent variability in gastric emptying. Upon contact with dissolution fluid, the plug swells and releases the drug after a delay. Another formulation features a four-layer spherical structure, including a swelling agent, drug, and an outer membrane that ruptures as the swelling force increases. Hydrogel plugs use polymers like hydroxypropyl methylcellulose, polymethyl methacrylate, and polyvinyl acetate. An alternative approach uses enteric-coated, timed-release press-coated tablets, with a core containing drugs like diltiazem hydrochloride. Patel and Patel modified the Pulsincap device with diclofenac sodium to target the colon, offering a time-dependent release that reduces early morning symptoms and provides prolonged therapeutic effects.

8.2 CODAS (Chronotherapeutic Oral Drug Absorption System)

In some situations, immediate drug release is not desirable, and a delay in drug action is required for various reasons. One such example is chronotherapy, where drug release is deliberately programmed to occur after a certain time following administration. To achieve this delayed release, Elan Drug Technology developed the CODAS (Controlled Onset Drug Absorption System) technology. The benefits of CODAS include a delivery profile that aligns with circadian rhythms, controlled onset, extended-release properties, and a release rate that is largely unaffected by factors such as pH, posture, or food intake. Additionally, the system allows for "sprinkle" dosing by opening the capsule and sprinkling the contents on food, reduces the effective daily dose and systemic drug exposure, targets the gastrointestinal tract for local effects, and ensures a target pharmacokinetic profile.

Verelan PM, which utilizes the CODAS technology, is designed for bedtime administration, with a 4- to 5-hour delay in drug delivery. This controlled-onset system ensures that the maximum plasma concentration (Cmax) of verapamil occurs in the morning. The capsule contains pellets that facilitate the extended release of the drug in the gastrointestinal tract. The Verelan PM formulation is designed to begin the release of verapamil 4–5 hours after ingestion. This delay is achieved by using a non-enteric release-controlling polymer applied to the drug-loaded beads. The polymer coating consists of both water-soluble and water-insoluble components. As water from the gastrointestinal tract comes into contact with the beads, the water-soluble polymer dissolves gradually, creating pores through which the drug diffuses. The water-insoluble polymer continues to act as a barrier, ensuring controlled release of the drug. Importantly, the release rate is largely independent of factors like pH, posture, and food intake. Multiparticulate systems like Verelan PM are also less influenced by gastrointestinal motility.

8.3 OROS Technology

The OROS delivery systems were developd to address the challenge of poorly water-soluble drugs. The push-pull system typically consists of a bilayer or trilayer tablet core, which includes a push layer and one or more drug layers. The drug layer contains the poorly soluble drug, osmotic agents, and a suspending agent. The push layer contains osmotic agents and

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water-swellable polymers. The tablet core is surrounded by a semipermeable membrane. Various OROS systems have been developed, including Procardia XL, Ditropan XL, and Concerta, which are prominent examples. A more recent innovation, the L-OROS SOFTCAP delivery system, combines controlled-release and bioavailability-enhancing features, improving both patient compliance and therapeutic efficacy.

L-OROS technology was specifically developed by Alza to solve issues related to drug solubility. These formulations use self-emulsifying liquid carrier formulations (SEF) that improve the absorption of the drug through the gastrointestinal membrane and bloodstream. The SEF in L-OROS systems consist of drugs in non-aqueous liquid carriers, which are formulated to form either a solution or a nanosuspension. When the drug in solution is released in the GI tract, it forms very small droplets (less than 100 nm), enhancing the drug's solubility and bioavailability. In the case of a nanosuspension, the drug nanoparticles are dispersed upon release, preventing aggregation and further improving the drug's bioavailability.

8.4 IPDAS Technology

The Intestinal Protective Drug Absorption System (IPDAS) is an oral drug delivery method designed for gastrointestinal irritant drugs, such as NSAIDs. It uses controlled-release beads compressed into a tablet. Upon ingestion, the tablet disintegrates in the stomach, releasing beads that gradually release the drug as they move through the gastrointestinal tract, independent of food intake. The polymer coating on the beads controls the drug release. IPDAS technology ensures the drug is widely dispersed, reducing local irritation. It was initially developed for Elan Drug Technologies' Naprelan (naproxen) formulation, providing a once-daily controlled-release option with fast pain relief onset (within 30 minutes) and reduced gastric irritation, lasting up to 24 hours.

8.5 Geoclock

Sky pharma developed Geoclock, an oral drug delivery system using chronotherapy-focused press-coated tablets. These tablets have an active drug core inside a hydrophobic wax and brittle outer layer, allowing for controlled, pH-independent drug release after a specific delay. This technology enables both slow and immediate drug release, as well as targeted drug delivery to the colon or multiple pulses throughout the day. Lodotra, a drug formulated with Geoclock, releases prednisone four hours after ingestion, with peak plasma levels occurring six hours later, making it ideal for treating early morning stiffness in rheumatoid arthritis by delivering the drug at the optimal time when inflammatory cytokines peak.

8.6 Uniphyl

Uniphyl (theophylline, anhydrous) tablets, which utilize a controlled-release system, enable a 24-hour dosing interval for patients. When administered with food, Uniphyl is fully absorbed following oral administration.

8.7 TMDS (Time Multiple Action Delivery System)

This system regulates the release rates of various ingredients within a single tablet in a controlled manner. TMDS technology enables the release of multiple active ingredients from a single tablet formulation at different times, following distinct release profiles over a set period.

8.8 Covera-HS

Covera-HS is the first once-daily formulation of an antihypertensive and anti-anginal drug that employs an advanced tablet coating and a novel drug delivery system to mimic the body's natural 24-hour circadian rhythms in blood pressure and heart rate. This unique technology, known as COER-24 (Controlled-Onset-Extended-Release), was developed in collaboration with Alza Corp. Covera-HS is currently the only controlled-release verapamil formulation approved for the treatment of both hypertension (high blood pressure) and angina pectoris (chest pain).

Available in 180 mg and 240 mg tablet doses, Covera-HS is intended to be taken orally at bedtime. The drug reaches its peak concentration during the early morning hours, coinciding with the period when blood pressure and heart rate naturally rise most rapidly. During sleep, when blood pressure and heart rate are at their lowest physiological levels, there is minimal drug release. This timing aligns with the body's natural circadian variations, optimizing the therapeutic effects of the medication.

8.9 OSDRC Technology

The traditional dry-coated tablet (DC) method involves preparing a core tablet first, making the process more complex. This increased complexity leads to higher manufacturing costs and a greater likelihood of failure, which can result in a need for additional core tablets. To address this issue, the One-Step Dry-Coated Tablet (OSDRC) technology was developed. This system uses a double-structure punch (with a center punch and an outer punch), allowing the dry-coated tablets to be formed in a single operation. The process consists of three stages: compressing the bottom layer (the first outer layer), compressing the core, and then performing a final compression to form the whole tablet, which includes the upper and side layers (the second outer layer). Since the tablets are produced in a single step with the punches completing one rotation on the turntable, there is no longer a need for a separate stage to add the core.

8.10 Diffutab

Diffutab technology allows for tailored drug release profiles and region-specific delivery. It uses a combination of waxes and hydrophilic polymers to regulate the release of the drug through diffusion and the erosion of the matrix tablet. Diffutabs are especially beneficial for high-dose medications and those requiring sustained release or once-daily dosing. Eurand has applied this technology to both soluble and insoluble products. Key benefits of Diffutabs include high drug loading, the ability to support sustained release, and the convenience of once-daily dosing, as the matrix tablets combine water-soluble particles with the active drug.

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9. CONCLUSION

The rapid advancements and recent developments in drug delivery technologies have led to the creation of pulsatile drug delivery systems. These systems offer a unique advantage, being both easy to formulate and capable of delivering substantial therapeutic benefits. By releasing the drug at the right time, in the right place, and in the correct amount, pulsatile systems ensure more precise and effective treatment. In particular, circadian disorders often require chronopharmacotherapy, which can be efficiently achieved with pulsatile drug delivery systems. Over the past two decades, pharmaceutical technology has made significant strides, and with the advent of pulsatile drug delivery, the goal of providing safe and effective therapy is more achievable than ever.

Certain medical conditions demand that drugs or bioactive compounds be delivered in a precise manner. Conventional dosage forms often cannot meet these requirements, or they do so only partially. By modifying and designing conventional delivery systems into pulsatile formats, it becomes possible to control the time-released delivery of active compounds, which is crucial in treating such conditions. The causes of many chronic diseases can be linked to the timing and release of specific drugs, and pulsatile drug delivery systems can significantly improve therapeutic outcomes. Although considerable progress has been made in this area, there are still untapped aspects of pulsatile drug delivery that could lead to new opportunities for more effective therapies through better system engineering.

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