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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 the field of pharmaceutical technology due to their ability to deliver drugs at specific times and sites, providing advantages over conventional dosage forms. These systems are designed to release a certain amount of drug rapidly and completely after a predetermined lag time or period of no drug release. This unique mechanism of drug release offers improved therapeutic efficacy and increased patient compliance. Pulsatile drug delivery systems ensure that the drug is delivered at the right time when the disease is most active or when the body's natural rhythms are disrupted. This targeted and time-controlled drug release is particularly useful for diseases or conditions that exhibit time-dependent variations in symptoms or require drug administration at specific times for optimal therapeutic outcomes. Coating technology and swellable/erodible polymers are commonly employed in pulsatile drug delivery systems to control drug release. Coating technology involves the use of a rupturable coating layer that acts as a barrier to drug release. This coating layer can be designed to dissolve or rupture in response to specific triggers such as changes in pH, temperature, or enzymatic activity, allowing for rapid and complete drug release. Swellable/erodible polymers, on the other hand, can control the release of drugs by gradually releasing them as they swell or erode over time. Swellable polymers absorb water and increase in volume, creating pores or channels for gradual drug release. Erodible polymers degrade over time, leading to the release of the drug from the matrix or hydrogel. Recent advances in pulsatile drug delivery systems have explored remotely controlled delivery systems. These systems utilize external stimuli such as magnetic fields or ultrasound to trigger drug release at a specific time or site, offering enhanced control and precision in drug delivery. In conclusion, pulsatile drug delivery systems offer a promising approach for targeted and time-controlled drug release. They have the potential to improve therapeutic outcomes, increase patient compliance, and minimize side effects associated with continuous or non-specific drug release. Further research and development efforts are needed to optimize these systems and translate them into clinical practice.

INTRODUCTIONS

Drug delivery systems play a critical role in the effective treatment of various diseases and conditions. Conventional drug delivery methods often fail to provide optimal therapeutic outcomes due to their inability to maintain a steady concentration of drugs in the body. Pulsatile drug delivery systems have emerged as a promising approach to overcome these limitations by providing targeted and time-controlled release of therapeutic agents[1].

Pulsatile drug delivery systems are designed to release drugs in a pulsatile manner, mimicking the natural physiological patterns of certain diseases or conditions. These systems can optimize therapeutic outcomes by releasing drugs during specific periods when the disease is most active or when the body's natural rhythms are disrupted. Pulsatile drug delivery systems offer several advantages over conventional drug delivery methods, including improved therapeutic efficacy, enhanced patient compliance, and minimized side effects.

Pulsatile drug delivery systems with time control are a specialized form of drug delivery systems that aim to release drugs in a pulsatile manner, meaning that the drug is released in a rapid and transient manner within a specific time period after a predetermined lag time or off-release period. These systems have a unique mechanism that allows for the rapid and complete release of the drug after a certain lag time, ensuring precise and targeted drug delivery[2].

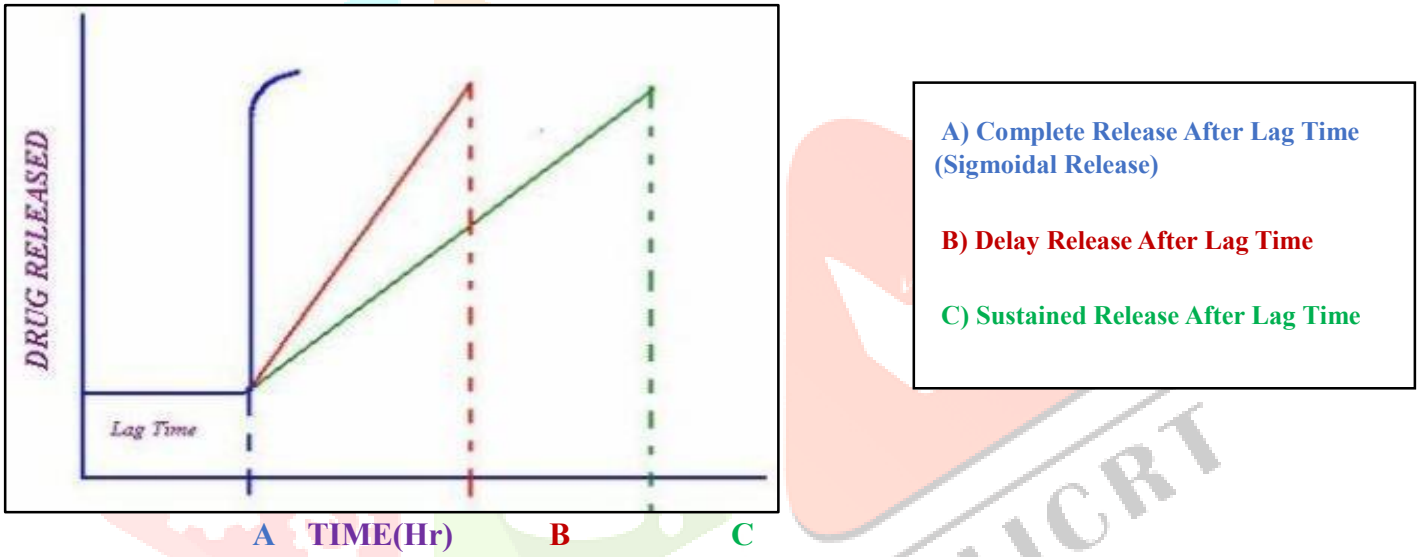

Fig 1. Representation of different drug delivery systems.

This review aims to provide a comprehensive overview of pulsatile drug delivery systems, including their types, mechanisms of action, advantages, and applications. The review will discuss various approaches utilized to achieve pulsatile drug release, such as time-dependent systems, stimuli-responsive systems, and externally triggered systems. Time-dependent systems rely on formulation design to control drug release at predetermined time intervals. Stimuli-responsive systems respond to specific physiological or environmental cues to trigger drug release. Externally triggered systems rely on external stimuli, such as magnetic fields or ultrasound, to initiate drug release. The review will highlight the importance of pulsatile drug delivery in the treatment of diseases that exhibit circadian rhythms or time-dependent variations in symptoms. Examples include asthma, cardiovascular disorders, hormonal imbalances, and certain types of pain. Pulsatile drug delivery can optimize therapeutic outcomes by releasing drugs during specific periods when the disease is most active or when the body's natural rhythms are disrupted. This approach can enhance drug efficacy and reduce side effects associated with continuous or non-specific drug release[3].

Diseases that require periodic pulsatile drug delivery systems prefer a pulse of therapeutic concentration rather than constant drug levels. These systems are designed to achieve rapid and transient release of a specific amount of drug molecules within a short time period, following a predetermined off-release period. Various techniques are available for achieving pulsatile drug delivery, including pH-dependent systems, time-dependent systems, and microflora-activated systems. These techniques can be tailored based on the physiology of the disease and the properties of the drug molecule. This review primarily focuses on pulsatile drug delivery methodologies

and emerging technologies that are being utilized on an industrial scale[4]. The review will also discuss the challenges and considerations in the development of pulsatile drug delivery systems. These include formulation stability, manufacturing techniques, regulatory aspects, and patient-specific factors. Achieving precise and reproducible pulsatile drug release poses technical challenges that require careful formulation design and optimization. Additionally, regulatory considerations must be addressed to ensure the safety and efficacy of these systems. In conclusion, pulsatile drug delivery systems hold great promise for improving the treatment of various diseases by providing targeted and time-controlled drug release. These systems offer advantages such as improved therapeutic efficacy, enhanced patient compliance, and minimized side effects. Further research and development efforts are needed to optimize pulsatile drug delivery systems and translate them into clinical practice. The advancement of nanotechnology and smart materials may provide new opportunities for the development of more sophisticated and precise pulsatile drug delivery systems[4]. Pulsatile drug delivery systems are required to address the limitations of conventional drug delivery methods, which often fail to provide optimal therapeutic outcomes. Conventional drug delivery methods, such as oral tablets or injections, typically provide a continuous or non-specific release of drugs. This can lead to suboptimal drug concentrations in the body, which may result in reduced therapeutic efficacy or increased side effects. Pulsatile drug delivery systems offer several advantages over conventional drug delivery methods. By releasing drugs in a pulsatile manner, these systems can mimic the natural physiological patterns of certain diseases or conditions. This can optimize therapeutic outcomes by releasing drugs during specific periods when the disease is most active or when the body's natural rhythms are disrupted. Pulsatile drug delivery can enhance drug efficacy and reduce side effects associated with continuous or non-specific drug release[5].

Need of pulsatile drug delivery systems[6]

Pulsatile drug delivery systems are particularly useful for diseases that exhibit circadian rhythms or time-dependent variations in symptoms. Examples include asthma, cardiovascular disorders, hormonal imbalances, and certain types of pain. In these cases, pulsatile drug delivery can release drugs during specific periods when the disease is most active or when the body's natural rhythms are disrupted. This approach can enhance drug efficacy and reduce side effects associated with continuous or non-specific drug release. Overall, pulsatile drug delivery systems are needed to provide targeted and time-controlled release of therapeutic agents. These systems offer several advantages over conventional drug delivery methods, including improved therapeutic efficacy, enhanced patient compliance, and minimized side effects. Further research and development efforts are needed to optimize pulsatile drug delivery systems and translate them into clinical practice.

There are several advantages of pulsatile drug delivery systems.

Here are some key advantages[7]:

1. Improved Therapeutic Efficacy: Pulsatile drug delivery systems release drugs in a targeted and time-controlled manner, optimizing drug concentrations at specific periods when the disease is most active or when the body's natural rhythms are disrupted. This can enhance the therapeutic efficacy of the drug.
2. Enhanced Patient Compliance: Pulsatile drug delivery systems can reduce the frequency of drug administration by providing a controlled release of drugs at specific time intervals. This can improve patient compliance as it minimizes the need for frequent dosing.
3. Minimized Side Effects: By releasing drugs in a pulsatile manner, these systems can help minimize side effects associated with continuous or non-specific drug release. Pulsatile drug delivery can ensure that drugs are released when they are needed most, reducing the exposure of the body to unnecessary drug concentrations.
4. Optimal Drug Concentrations: Pulsatile drug delivery systems can maintain drug concentrations within the therapeutic range for a specific period, maximizing the drug's effectiveness. This can lead to better treatment outcomes compared to conventional drug delivery methods.
5. Tailored to Circadian Rhythms: Diseases or conditions that exhibit circadian rhythms or time-dependent variations in symptoms can benefit from pulsatile drug delivery. These systems can release drugs during specific periods when the disease is most active, aligning with the body's natural rhythms and optimizing treatment.
6. Flexibility in Drug Release Profiles: Pulsatile drug delivery systems offer flexibility in designing drug release profiles. Different approaches, such as time-dependent systems, stimuli-responsive systems, or

externally triggered systems, allow for customization of drug release patterns based on specific therapeutic needs.

7. Potential for Reduced Dosing Frequency: With pulsatile drug delivery systems, drugs can be released at precise intervals, allowing for reduced dosing frequency compared to conventional continuous release systems. This can improve patient convenience and adherence to the treatment regimen.
8. Targeted Delivery: Pulsatile drug delivery systems can be designed to target specific sites or tissues in the body, minimizing systemic exposure and potential side effects on non-targeted areas.
9. Opportunities for Combination Therapy: Pulsatile drug delivery systems can facilitate the delivery of multiple drugs or therapeutic agents with different release profiles, enabling combination therapy and synergistic effects.
10. Potential for Personalized Medicine: Pulsatile drug delivery systems can be tailored to individual patient needs, considering factors such as circadian rhythms, disease progression, and patient-specific variations in drug response.

Overall, pulsatile drug delivery systems offer several advantages that can improve therapeutic outcomes, enhance patient compliance, and minimize side effects compared to conventional drug delivery methods.

Disadvantages of Pulsatile drug delivery system[8]

While pulsatile drug delivery systems offer several advantages, there are also some disadvantages to consider. Here are a few:

1. Complexity in Formulation Design: Developing pulsatile drug delivery systems can be technically challenging. Achieving precise and reproducible pulsatile drug release requires careful formulation design and optimization. Formulating the drug and controlling its release in a pulsatile manner can be complex and may require specialized manufacturing techniques.
2. Limited Drug Compatibility: Some drugs may not be suitable for pulsatile drug delivery systems due to their chemical properties or stability concerns. Certain drugs may degrade or lose efficacy when exposed to the formulation components or the pulsatile release mechanisms.
3. Manufacturing Challenges: The manufacturing process for pulsatile drug delivery systems can be more complex and costly compared to conventional drug delivery systems. Specialized equipment and techniques may be required, which can add to the production costs and limit scalability.
4. Regulatory Considerations: Pulsatile drug delivery systems may face regulatory challenges due to their unique release profiles and mechanisms. Additional studies and data may be required to demonstrate the safety, efficacy, and consistency of these systems, which can prolong the regulatory approval process.
5. Patient Variability: Pulsatile drug delivery systems may not be suitable for all patients, as individual variations in disease patterns or circadian rhythms can affect the effectiveness of the pulsatile release. Tailoring the pulsatile drug delivery to individual patients may require additional customization or monitoring.
6. Limited Applications: Pulsatile drug delivery systems may not be applicable to all diseases or conditions. While they are particularly useful for diseases with time-dependent variations or circadian rhythms, their utility may be limited in conditions that do not exhibit such patterns.
7. Potential for Missed Doses: In some cases, if the timing of drug release does not align with the disease activity or patient's lifestyle, there is a risk of missed doses. This could lead to suboptimal therapeutic outcomes if the drug is not released during the critical periods.
8. Cost Considerations: Pulsatile drug delivery systems may have higher development and manufacturing costs compared to conventional drug delivery methods. These costs could potentially limit their accessibility and affordability, affecting their widespread adoption.

It's Important to note that while these disadvantages exist, ongoing research and innovation in the field of pulsatile drug delivery aim to address these challenges and further optimize the technology for improved therapeutic outcomes.

Diseases that required pulsatile drug delivery system[9]

A thorough understanding of disease physiology is crucial when designing pulsatile drug delivery systems. Certain diseases exhibit rhythmic circadian organization, leading to fluctuations in the pharmacokinetics and/or pharmacodynamics of drugs within a 24-hour period. Table 1 provides examples of diseases that demonstrate such chronological behaviour.

One disease where pulsatile drug delivery systems can be beneficial is asthma. Normal lung function experiences circadian changes, reaching its lowest point in the early morning hours. In cardiovascular diseases, various functions of the cardiovascular system, such as blood pressure, heart rate, stroke volume, cardiac output, and blood flow, follow circadian rhythms. For instance, capillary resistance and vascular reactivity are higher in the morning and decrease later in the day. Morning hours are associated with increased platelet aggregability and decreased fibrinolytic activity, resulting in a state of relative hypercoagulability of the blood. In diabetes, there are well-studied circadian variations in glucose and insulin levels. This has clinical implications, particularly in the case of insulin substitution in type 1 diabetes. Additionally, circadian changes in lipid fractions can contribute to alterations in other metabolisms and the blood coagulation system, leading to various complications. Hepatic cholesterol synthesis also follows a circadian rhythm.

In the case of arthritis, there is a circadian rhythm in the plasma concentration of C-reactive protein and interleukin-6 in patients with rheumatoid arthritis.

Table 1. **Diseases that required pulsatile drug delivery system**

Chronological behaviour	**Diseases**	**Drug Used**
Acid secretion elevated in night and after noon	Peptic ulcer	Proton pump Inhibitors
Attack of Asthma during night or at early morning	Asthma	Beta 2 agonist
Blood pressure rises during early morning	Hypertension	ACE Inhibitors
Pain increases at night.	Arthritis	NSAIDs, Glucocorticoids
Increase in the blood sugar level after meal.	Diabetes Mellitus	Insulin
Cholesterol synthesis is generally higher during night than day time.	Hypercholesterolemia	HMG- COA reductase inhibitors
Increase in DOPA level in afternoon.	Attention deficit syndrome	Methylphenidate

Method for Pulsatile Drug Delivery System[10]

Methodologies for the pulsatile drug delivery system can be broadly classified into four classes;

1. Time controlled

2. Stimuli induced

3. Externally regulated

4. Multi particulate

There are several approaches utilized for pulsatile drug delivery systems. Here are some common approaches:

1. **Time controlled pulsatile release system:** Time-controlled pulsatile release systems are a type of drug delivery system designed to release drugs at specific predetermined time intervals. These systems are particularly useful for diseases or conditions that exhibit time-dependent variations in symptoms or require drug administration at specific times for optimal therapeutic efficacy. The design of time-controlled pulsatile release systems involves the use of various techniques to delay or control drug release until the desired time. Some common approaches include:

A) Coating technology[11]: Delivery systems with rupturable coating layers are a type of drug delivery system designed to release drugs by breaking or rupturing a coating layer surrounding the drug formulation. These systems are commonly used to achieve targeted and controlled drug release at specific sites or in response to specific triggers.

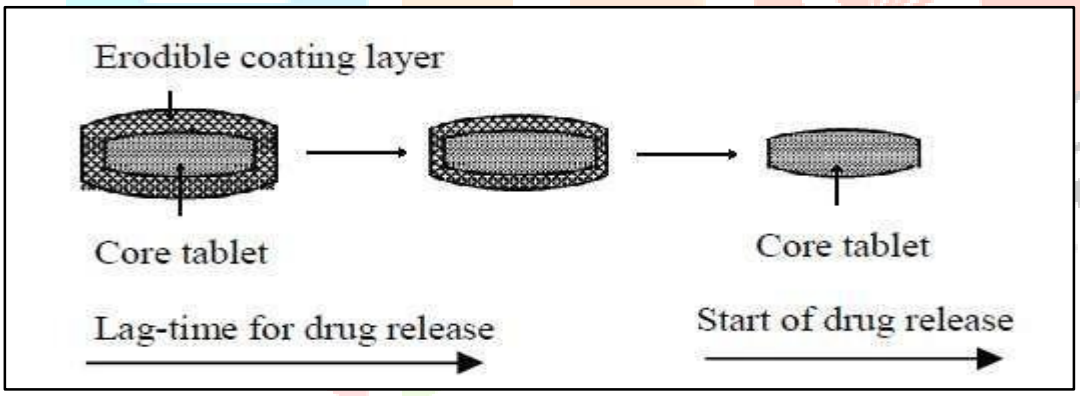

Fig 2. Drug delivery with erodible coating layer

The key characteristic of these delivery systems is the presence of a coating layer that acts as a barrier to drug release. This coating layer can be made of various materials, such as polymers, lipids, or proteins, and is designed to provide protection and control over the drug release process.

When the desired condition or trigger is met, such as a change in pH, temperature, or enzymatic activity, the coating layer is ruptured or dissolved, allowing the drug to be released. This can be achieved through various mechanisms, including:

- pH-sensitive coatings: The coating is designed to be stable at certain pH levels but dissolves or ruptures when exposed to a specific pH range, such as the acidic environment of the stomach or the alkaline environment of the intestines.
- Temperature-sensitive coatings: The coating is designed to remain intact at normal body temperature but dissolves or ruptures when exposed to higher or lower temperatures, such as at the site of inflammation or in hyperthermic conditions.
- Enzyme-sensitive coatings: The coating is designed to be stable in the presence of certain enzymes but breaks down or is cleaved by specific enzymes present at the target site. This allows for site-specific drug release.

B) Swellable or erodible systems: Swellable or erodible polymer-based time-controlled release systems are a type of drug delivery system that utilize polymers capable of swelling or eroding over time to control the release of drugs. These systems are designed to release drugs in a controlled and sustained manner, providing therapeutic effects over an extended period. In these systems, the drug is typically encapsulated or embedded within a polymer matrix or hydrogel. The polymer matrix or hydrogel is formulated using swellable or erodible polymers that can absorb water and undergo changes in their physical properties over time.

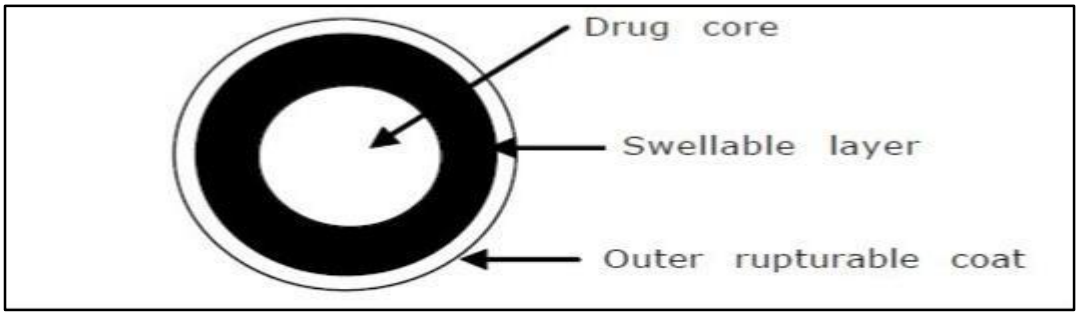

Fig 3. Drug delivery with Rupturable coating layer

Swellable polymers absorb water and increase in volume, causing the matrix or hydrogel to swell. This swelling action creates pores or channels within the polymer structure, allowing the drug to diffuse out gradually. The rate of drug release can be controlled by adjusting the polymer composition, crosslinking density, or the presence of additional release-controlling agents s[12].

Erodible polymers, on the other hand, undergo gradual degradation or erosion when exposed to physiological conditions. As the polymer degrades, the drug is gradually released from the matrix or hydrogel. The degradation rate of the polymer can be tailored by selecting suitable polymers and adjusting their molecular weight or composition. The advantage of swellable or erodible polymer-based time-controlled release systems is their ability to provide sustained and controlled drug release profiles. By selecting appropriate polymers and optimizing the formulation, these systems can be designed to release drugs over specific time periods, ranging from hours to days or even weeks. Such systems find applications in various therapeutic areas, including chronic conditions requiring long-term drug administration, where maintaining constant drug levels is essential for optimal therapeutic outcomes[13].

C) Capsule shaped system provided with release controlling plug: The proposed dosage form comprises an insoluble capsule body that contains a drug, along with swellable and degradable plugs composed of approved materials like hydrophilic polymers or lipids. A release-controlling plug is positioned between the immediate release compartment and the pulsed release compartment. When exposed to aqueous fluids, the capsule dissolves quickly, leading to the release of the immediate release component. Subsequently, the pulsed release component is released. The duration of the lag time is determined by the length of the plug[14,15].

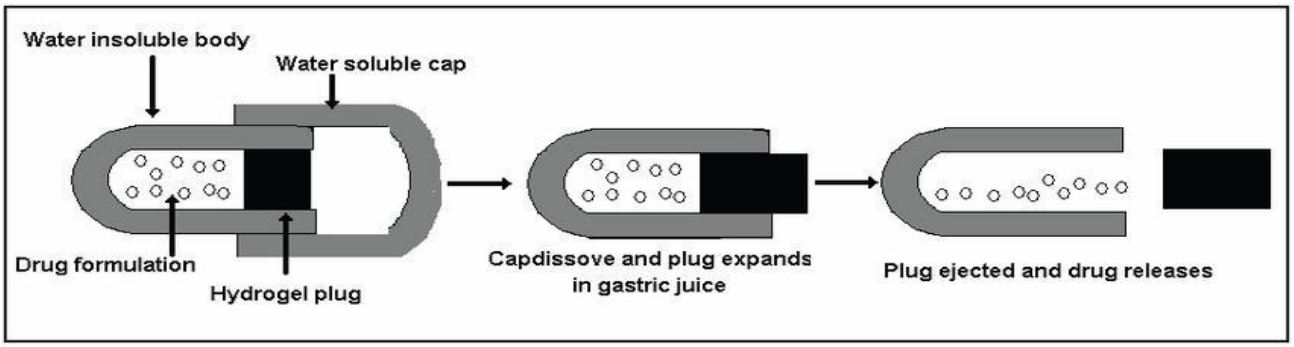

Fig 4. Release of drug from capsule

D)Pulsatile system based on Osmosis: A pulsatile drug delivery system based on osmosis utilizes the principles of osmotic pressure to achieve controlled and pulsatile drug release. This system typically consists of an osmotic core, a semi-permeable membrane, and a drug reservoir. The osmotic core contains an osmotic agent, such as a water-soluble salt or sugar, which creates an osmotic pressure gradient when exposed to water or body fluids. The drug reservoir, located within the core, contains the drug formulation to be delivered. Surrounding the osmotic core is a semi-permeable membrane that allows water or body fluids to enter the

system while preventing the passage of the drug molecules. This membrane acts as a controlled-release barrier[16].

When the osmotic system comes into contact with water or body fluids, it creates an osmotic pressure difference across the semi-permeable membrane. This pressure difference drives the influx of water into the system through the membrane. As water enters the osmotic core, it dissolves the osmotic agent, forming a concentrated solution. The increase in volume due to water influx leads to the expansion of the osmotic core. The expansion of the osmotic core exerts pressure on the drug reservoir, causing the drug formulation to be pushed out through a small orifice or delivery port in a pulsatile manner. This pulsatile release is driven by the periodic influx of water and subsequent expansion of the osmotic core. By adjusting the properties of the semi-permeable membrane, such as its thickness or permeability, and the formulation of the osmotic agent, the release rate and pulsatile behavior can be controlled[17].

2. Stimuli-induced pulsatile: These systems are designed to release the drug in response to specific biological factors or stimuli, such as temperature or chemical signals. They can be classified into two categories: temperature-induced systems and chemical stimuli-induced systems, based on the type of stimulus that triggers the drug release[18].

There are several types of stimuli that can be utilized to trigger pulsatile drug release, including[19]:

- Temperature: Temperature is a commonly used trigger for various types of triggered or pulsatile drug delivery systems. This is because the body temperature can deviate from the normal physiological temperature (37°C) in the presence of pathogens or pyrogens. This temperature deviation can serve as a useful stimulus to activate the release of therapeutic agents from temperature-responsive drug delivery systems, particularly for diseases associated with fever. Thermal stimuli-regulated pulsed drug release is achieved through the design of drug delivery devices such as hydrogels and micelles. These systems are designed to respond to changes in temperature, leading to controlled and pulsatile drug release.
- pH: pH-sensitive polymers, also known as polyelectrolytes, contain weak acidic or basic groups in their structure that can accept or release protons based on changes in environmental pH. These polymers exhibit pH-dependent behaviour and are commonly used in drug delivery systems. Examples of pH-sensitive polymers include cellulose acetate phthalate, polyacrylates, and sodium carboxymethyl cellulose[20].
- Light: Light-sensitive systems employ materials that can be activated or deactivated by specific wavelengths of light. Light triggers a chemical or physical change in the system, resulting in drug release.
- Enzymes: Enzyme-sensitive systems utilize enzymes present in specific biological environments to trigger drug release. The system may incorporate enzyme-responsive polymers or coatings that degrade or undergo conformational changes in the presence of specific enzymes, leading to drug release.

3. Externally regulated pulsatile release system[21]: Externally regulated pulsatile release systems are drug delivery systems that allow for controlled and on-demand drug release through external stimuli or triggers. These systems provide flexibility in drug administration, enabling precise control over the timing and dosage of drug release.

There are several methods used to externally regulate pulsatile drug release:

- Magnetic field: Magnetic field-responsive systems utilize magnetic materials incorporated into the drug delivery system. By applying an external magnetic field, the magnetic materials respond and trigger drug release.
- Electric field: Electric field-responsive systems utilize electrically conductive or responsive materials. By applying an external electric field, the system can be stimulated to release the drug.
- Ultrasound: Ultrasound-responsive systems utilize ultrasound waves to induce drug release. The system may contain materials that respond to ultrasound energy by undergoing physical or chemical changes, resulting in drug release.

- Light: Light-responsive systems use specific wavelengths of light to trigger drug release. By exposing the system to light of a particular wavelength, the materials within the system undergo changes, leading to drug release.
- Temperature: Temperature-responsive systems can be externally regulated by applying heat or cooling to induce drug release. By altering the temperature of the system, the materials within it can undergo changes that result in drug release.

Externally regulated pulsatile release systems offer advantages such as precise control over drug release, flexibility in dosing, and the ability to adapt to specific patient needs or treatment requirements. They have applications in various fields, including personalized medicine, chronotherapy, and targeted drug delivery.

4. Multi particulate pulsatile drug delivery system: The purpose of developing multiparticulate dosage forms is to create a reliable formulation that combines the benefits of a single unit formulation while avoiding the risk of altering the drug release profile and formulation behavior due to unit-to-unit variation. The release of the drug from microparticles is influenced by various factors, including the choice of carrier for forming the multiparticles and the drug content within them[22].

4.1 Reservoir systems with rupturable polymeric Coatings: Multiparticulate systems commonly consist of reservoir devices that are coated with a polymeric layer designed to rupture. When water enters the system, the pressure within increases, leading to the rupture of the polymer layer and subsequent release of the drug from the core. The use of swelling agents, gas-producing effervescent excipients, or increased osmotic pressure can help achieve the necessary pressure to rupture the coating. The lag time in drug release is influenced by factors such as water permeation and mechanical resistance of the outer membrane[23].

4.2 Reservoir systems with soluble or eroding Polymer coatings: A different type of multiparticulate pulsatile system utilizes soluble or erodible layers instead of rupturable coatings. In these systems, the barrier layer dissolves or erodes after a predetermined lag time, resulting in a burst release of the drug from the reservoir core. The lag time before drug release can generally be controlled by adjusting the thickness of the coating layer. However, it is important to note that since the release mechanism in these systems is dissolution, a higher ratio of drug solubility relative to the dose amount is necessary for rapid drug release after the lag period[24].

4.**3 Floating multiparticulate pulsatile systems:** Multiparticulate pulsatile release dosage forms, as mentioned earlier, have a longer residence time in the gastrointestinal tract (GIT). However, due to the highly variable nature of the gastric emptying process, there may be poor in vitro-in vivo correlation and bioavailability issues. On the other hand, floating multiparticulate pulsatile dosage forms remain in the stomach and are not affected by pH variability, local environment, or gastric emptying rate. These dosage forms are particularly advantageous for drugs that are absorbed from the stomach or require targeted delivery in the stomach. As a result, multiparticulate pulsatile release dosage forms with gastric retention capabilities have been developed to address these considerations[25].

CONCLUSION

The rapid progress and recent advancements in drug delivery have paved the way for the development of pulsatile drug delivery systems. These systems offer several advantages, including ease of formulation and the ability to provide precise therapeutic benefits. Pulsatile drug delivery systems ensure that the drug is delivered at the right time, in the right place, and in the right amount within the patient's body. This is particularly beneficial for circadian disorders that require chronopharmacotherapy. Pulsatile drug delivery systems enable the organized and controlled release of drugs in a manner that aligns with the patient's specific needs. Future research and development efforts are focused on advanced formulation technologies, personalized medicine approaches, integration of smart technologies, and combination therapies. These advancements hold promise for further improving the effectiveness and versatility of pulsatile drug delivery systems in the future

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