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PULSATILE DRUG DELIVERY SYSTEM- A REVIEW

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Abstract:

Pulsatile-release delivery systems are gaining popularity for the development of medications for which conventional controlled-release systems with a continuous release are ineffective. Pulsatile Drug Delivery Systems are gaining popularity because they deliver the drug to the appropriate place, at the right time, and in the right amount, ensuring spatial and temporal delivery while also boosting patient compliance. Humans have endogenous circadian rhythms that are controlled by the body's master circadian clock. The drug release profile of the product is sigmoidal, with a period of no release (lag time) followed by quick and total drug release. are not consistent, but change through time. Despite the fact that much drug delivery research has focused on constant drug release rates due to the limitations of delivering drugs according to disease rhythmicity, clinical studies show that the magnitude of rhythmic differences can be a significant predictor of when the most morbid and mortal events will occur during a 24-hour period.

The range of systems and approaches that can be used to deliver therapeutics is growing and advancing at an incredible rate, so learning about the advances in drug delivery has important implications for anyone working in health care and related sectors. Currently, Pulsatile drug delivery is gaining cumulative attention as it offers a more sophisticated approach to the traditional sustained drug delivery, a constant amount of drug released per unit time or constant blood levels. Pulsatile drug delivery aims to release drugs on a programmed pattern i.e.: at appropriate time and/or at appropriate site of action.

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INTRODUCTION:

Pulsatile-release delivery systems are gaining popularity for the development of medications for which conventional controlled-release systems with a continuous release are ineffective. Pulsatile Drug Delivery Systems are gaining popularity because they deliver the drug to the appropriate place, at the right time, and in the right amount, ensuring spatial and temporal delivery while also boosting patient compliance. Humans have endogenous circadian rhythms that are controlled by the body's master circadian clock. The drug release profile of the product is sigmoidal, with a period of no release (lag time) followed by quick and total drug release. are not consistent, but change through time. Despite the fact that much drug delivery research has focused on constant drug release rates due to the limitations of delivering drugs according to disease rhythmicity, clinical studies show that the magnitude of rhythmic differences can be a significant predictor of when the most morbid and mortal events will occur during a 24-hour period. Drugs that cause biological tolerance require a method that prevents them from remaining in the BioPhase indefinitely, as this reduces their therapeutic impact. Medicines that degrade in stomach acidic medium (e.g., peptide drugs) and irritate the gastric mucosa or cause nausea and vomiting require a lag period. For medications with a lower bioavailability due to first-pass metabolism, slow drug release from constant-release devices can lead to further degradation. Continuous exposure to drugs with more harmful effects may result in an increase in unfavorable effects. Constant exposure to medications that display tolerance reduces the drug's effect. In the contemporary pharmaceutical research and development field, modified release dosage forms have gained a lot of traction. Depending on the type, these dosage forms have varied release characteristics. This dose type refers to items that vary the timing and rate of medication material delivery.

A pulsatile release profile, in which the drug is released completely after a defined lag time, is advantageous for several drugs or therapies, including drugs that develop biological tolerance, drugs with extensive first pass metabolism, drugs targeted to a specific site in the intestinal tract, such as the colon, protecting the drug from degradation, and drugs that adapt drug needs to circadian rhythms of body functions or diseases.

There are several approaches to pulsatile drug delivery. Most systems have a drug reservoir that is surrounded by a barrier that erodes, dissolves, or ruptures. A potential issue with eroding or dissolving systems is the retardation and thus not immediate drug release following the loss of the barrier function or a premature release, which is seen in particular with highly water-soluble drugs.

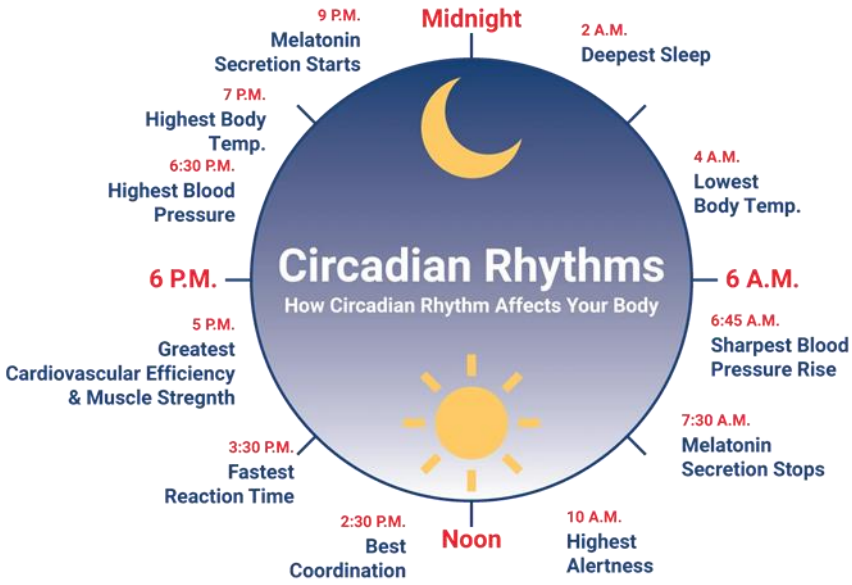
Various pathophysiological processes occur only at specific times of the day or at specific intervals of time in healthy humans. Exacerbation of disease has also been observed to follow a circadian rhythmic pattern. With knowledge of the time when the disease exhibits peak and trough phenomena, dosage forms can be designed in a time-controlled manner to maximize drug response while minimizing side effects.

Multiple body systems in humans are regulated by the circadian rhythm, including metabolism, physiology, behaviors, sleep patterns, hormone synthesis, and so on. During the morning hours, numerous shocks and heart attacks have been reported. Cortisol levels are greater in the morning, and its release is said to gradually decrease during the day. Blood pressure is also said to be high in the morning till late afternoon, then declines during the evening. Patients with osteoarthritis report having less pain in the morning than at night, but those with rheumatoid arthritis report having more pain in the morning. The release of medications in pulses is preferred to treat certain disorders. A single dosage form delivers an initial dose of drug followed by one release-free interval, followed by a second dose of drug, another release-free interval, and a pulse of drug release. The pulsatile drug delivery method has a number of advantages, including increased daytime or nighttime activity, less side effects, lower dosing frequency, and smaller doses. Patient compliance has improved. Because fewer dose units are required by the patient in therapy, there is a lower daily cost to the patient. Drug adjusts to biological processes or diseases' circadian rhythms. Drugs that target a specific organ, such as the colon, Mucosa protection from irritant medications Extensive first-pass metabolism prevents drug loss.

As a result, there has been a growing interest in the development of pulsatile drug delivery systems, which have a number of advantages over traditional dosage forms for the treatment of diseases such as hypertension, angina pectoris, myocardial infarction, asthma, ulcers, and rheumatoid arthritis, among others.

Continuous exposure to drugs with more harmful effects may result in an increase in unfavorable effects. Constant exposure to medications that display tolerance reduces the drug's effect. In the contemporary pharmaceutical research and

development field, modified release dosage forms have gained a lot of traction. Depending on the type, these dosage forms have varied release characteristics. This dose type refers to items that vary the timing and rate of medication material delivery.



According to the human body's circadian rhythm, pulsatile drug delivery systems (PDDS) are designed to release the medicine in the appropriate place, at the right time, and in the right amount. The suprachiasmatic nucleus, which is located at the base of the hypothalamus, regulates the circadian rhythm (24-hour cycle) that occurs in various physiological processes. As a result, synchronizing biological cycles with medical treatment could deliver maximal health advantages while causing the least amount of harm to the patient.

The term "chronotherapy" refers to this type of medical treatment.

The goal of medication development is to achieve optimum drug efficacy while minimizing negative effects. Drug therapy has taken a different path as a result of technological advancements in the pharmaceutical business. When compared to immediate release drug delivery systems, controlled release drug delivery systems have a number of advantages, including a nearly constant drug level in the plasma, minimal peak-trough fluctuations, avoidance of undesirable side effects, reduced dose, reduced frequency of administration, and improved patient compliance. Biological systems are not as receptive to these release mechanisms, despite the fact that sustained and regulated release methods have been devised. Furthermore, in some circumstances, such as time-programmed hormone administration and many medications that follow a chronotherapeutic regimen, sustained and controlled release devices are ineffective. Metabolic enzymes can rapidly breakdown certain hormones and medicines, and resistance can develop.

Advantages of pulsatile drug delivery system:

- Drug loss is avoided due to extensive First pass metabolism.
- Extended daytime or nighttime activity.
- Flexibility in design Achieve a unique release pattern.
- Improved bioavailability, stability, patient comfort and compliance.
- Improved tolerability
- It also provides target specific action to colon.
- It is feasible to maintain dosage frequency.
- Limited risk of local irritation
- No risk of dose dumping
- Patient compliance increases due to low dose and minimum dosage frequency.
- Pulsatile drug delivery system has a fewer side effect.
- Reduced adverse effects
- This technology reduces dose size.

Necessity of pulsatile drug delivery systems:

1. Human body follows circadian rhythm (their functions depend on time)

2. It is useful in case of drugs that undergoes extensive first pass metabolism.
3. Many of diseases like bronchial asthma, myocardial infarction, angina pectoris, peptic ulcer, and hypertension are time dependent.
4. Most of the drugs produces biological tolerance and hence there is demand for a system that will prevent their continuous presence at the site of action. E.g., Salbutamol sulphate.

Drawbacks of pulsatile delivery:

1. It needs advanced technology.
2. It requires multiple steps for formulation.
3. Manufacturing reproducibility and efficacy is less.
4. There are large number of process variables.

Pulstatile drug delivery system:

A modified release pattern of the active components from the dosage form in which aliquots of the whole dose are released at two or more-time intervals. After a defined lag period, pulsatile drug delivery methods release the active component entirely and quickly. Pulsatile drug delivery is medication delivery that is time and place specific, allowing for spatial and temporal delivery while also boosting patient compliance. Pulsatile drug delivery is defined as the rapid and transient release of a specific number of molecules in a short time period after a predetermined off-released period, i.e., lag time, or these systems have a unique mechanism for rapidly and completely delivering the drug after a lag time, i.e., no drug release period. Pulsatile release is a term for this type of release pattern.

EXPERIMENTAL MATERIAL AND METHODS:

To generate the pulsatile release of medicinal drugs, two alternative techniques have been examined. The development of preprogrammed delivery systems, in which the medicine is administered at a predetermined moment or in a known sequence of pulses, is one way. The creation of a system that responds to certain inputs is a second way.

Pulsatile Drug Delivery System Classification (PDDS)

There are two systems in the PDDS.

A. Pre-Planned System B. Stimulus Induced Systems

A. <u>Pre-planned systems</u>

1. Pulsatile system based on capsule.
2. Pulsatile system based on osmosis.
3. Drug delivery system with erodible or soluble layer.
4. Drug delivery system with rupturable layer

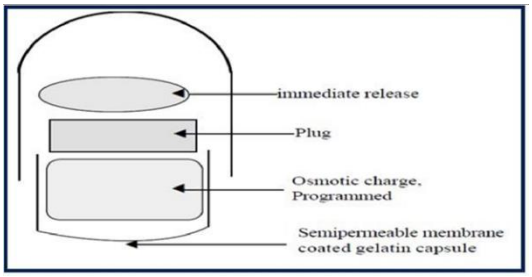
Pulsatile System Based on Capsule:

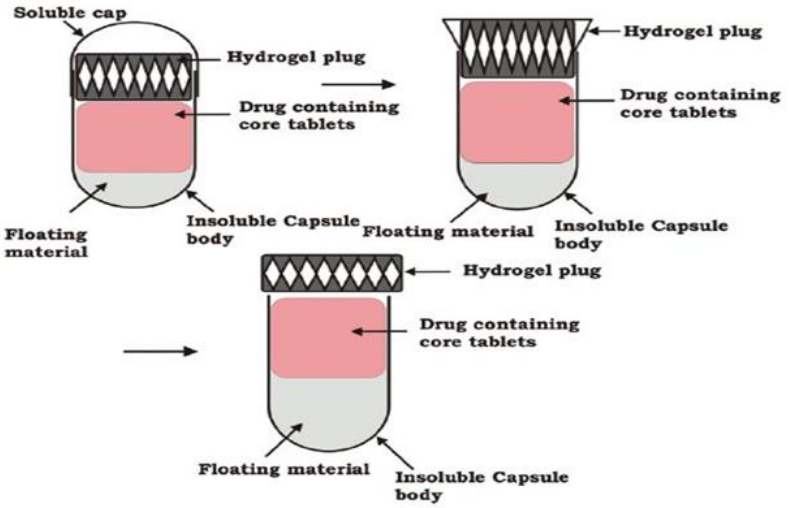
PulsincapTM system, which consists of an insoluble capsule body and swellable and degradable plugs comprised of authorized substances such as hydrophilic polymers or lipids, is a capsule-based system. The lag time is controlled by a plug that is forced away from the insoluble capsule by swelling or erosion, and the medication is released as a pulse from the PulsincapTM®. The medicine contents are sealed in the capsule body by a swellable hydrogel stopper. The hydrogel plugs swell when this capsule body comes into contact with the dissolution media, and after a lag time, the plug. regulated pulsatile release. An enteric polymer is used in one of the coated membranes, while a mixture of water-insoluble polymer and an enteric polymer is used in the other. The lag time and duration of drug release from each of the bead populations are determined by the composition and thickness of the polymeric membranes.

Pulsatile System Based on Osmosis:

The osmotic system consists of a capsule coated with a semipermeable membrane. The capsule contained an insoluble plug, an osmotically active agent, and the drug formulation. When this capsule came into contact with body fluid, the semipermeable membrane allowed water to enter, causing pressure to build and the insoluble plug to be expelled due to pressure after some lag time. An osmotic capsule was developed, which consists of a hard gelatin capsule filled with acetaminophen, an osmotic agent (sorbitol), a release promoter (sodium dodecyl sulphate), coated with a semipermeable cellulose acetate membrane containing a hydrophobic plasticizer (castor oil), and sealed with white bee wax. When placed in sink water, it penetrates the membrane, dissolves the osmotic agent, and increases the osmotic agent inside the capsule. The increased osmotic pressure increases water absorption and, as a result, the hydrostatic pressure inside the capsule, which, when high enough, expels the plug and the drug release begins. The lag time (t L) between the onset of drug imbibition and the thickness of the semipermeable membrane and the thickness of the plug depends on the thickness of the semipermeable membrane and the thickness of the plug. It was developed to deliver agents via osmotic systems based on expandable orifice technology. The system consists of a capsule from which the drug is delivered via osmotic infusion of moisture from the body. To generate a pulsatile delivery effect, the delivery orifice opens and closes intermittently. The aperture forms in the capsule wall, which is made of an elastic material, ideally an elastomer (e.g., styrene-butadiene copolymer), and extends when the pressure inside the

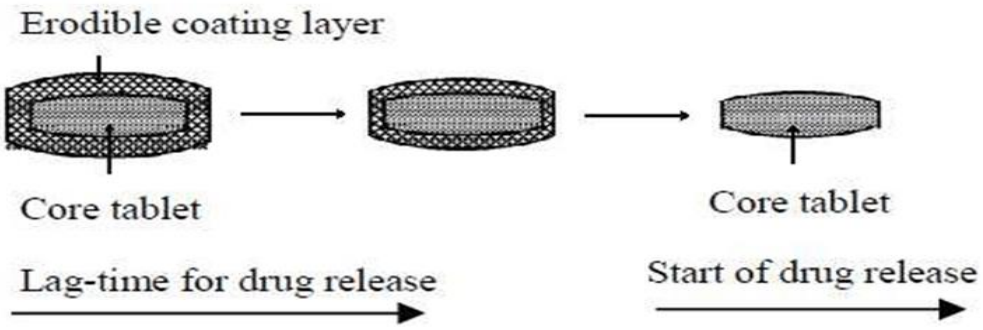
capsule rises. The aperture is tiny enough that the drug flow rate through the opening is nearly zero when the elastic wall is relaxed. The aperture expands enough to allow the medication to be released at a physiologically needed rate when the elastic wall is stretched due to a pressure differential across the wall surpassing a threshold.

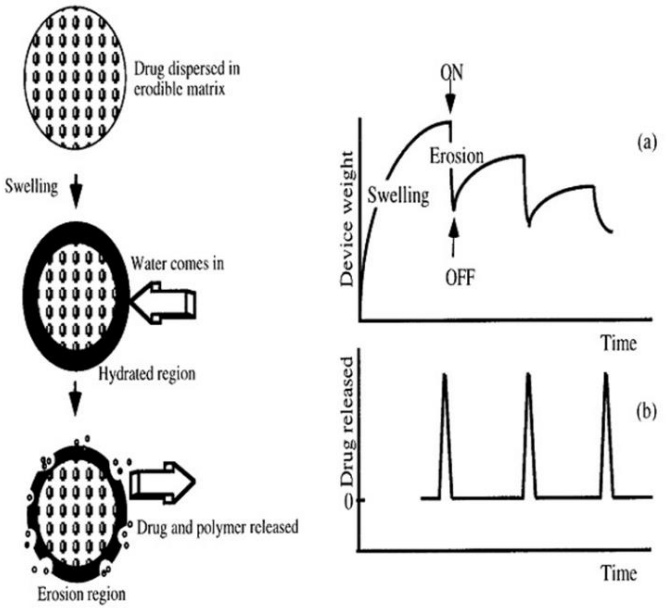




Drug Delivery System with Erodible or Soluble Layer The disintegration or erosion of the outer coat applied to the core carrying the drug controls the drug release in such systems. By optimizing the thickness of the outer coat, time-dependent release of the active ingredient can be achieved, for example, in a chronotropic system, which comprises of a drug-containing core laminated with HPMC and optionally covered with an outer enteric coating. The thickness and viscosity grade of the HPMC layer determine the time between medication release and release. The time clock system is an aqueous dispersion-coated solid dosage form delivery device. This coating consists of a hydrophobic surfactant layer with a water-soluble polymer added to promote core adherence. The dispersion rehydrates and redisperses once it comes into touch with the dissolution fluid. The thickness of the film could be changed to alter the lag time.

In vitro and in vivo, this system has produced consistent findings. Gamma scintigraphy was used to investigate the influence of a low-calorie and a high-calorie meal on the lag time. The average drug release lag time was 345 and 333 minutes, respectively.

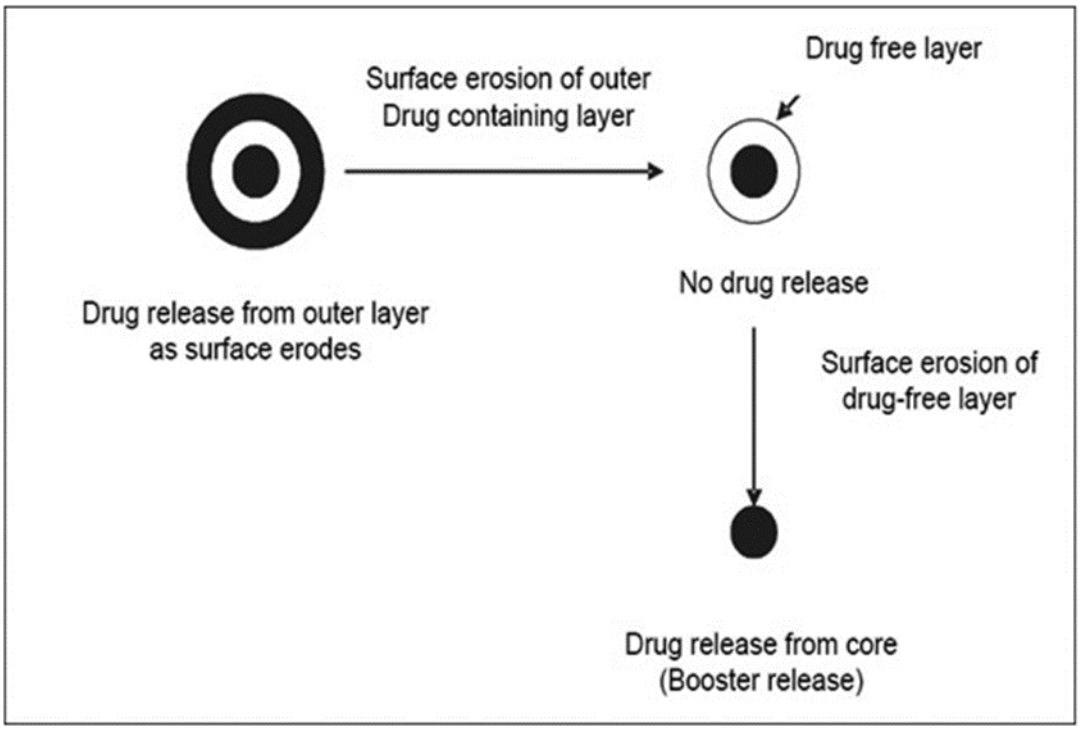




Pulsatile drug release from erodible matrix

Drug Delivery System with Rupturable Layers/ Membranes:

These systems are made up of a water-insoluble yet permeable outer release that is subject to mechanically induced rupture. Various systems based on hard gelatin capsules and tablet cores have recently been disclosed, all of which are coated with an inner swellable and outer rupturable layer. Swelling, osmotic, or effervescent additives in the reservoir might cause the film to burst. Bussemer et al. developed a pulsatile device using a rupturable coating on a medication that was contained in hard gelatin capsules. These capsules were coated with a swelling layer initially, followed by an insoluble yet water-permeable outer layer. When submerged in the release medium, these coated capsules could take up the media at a consistent pace until the outer coating ruptured due to the pressure created by the swelling layer. It was concluded that the lag time may be reduced by increasing the swelling layer. The lag time could be extended by increasing the outer covering. The addition of HPMC to the outer layer was also shown to reduce the lag time.



Release of a drug from a Surface eroding system

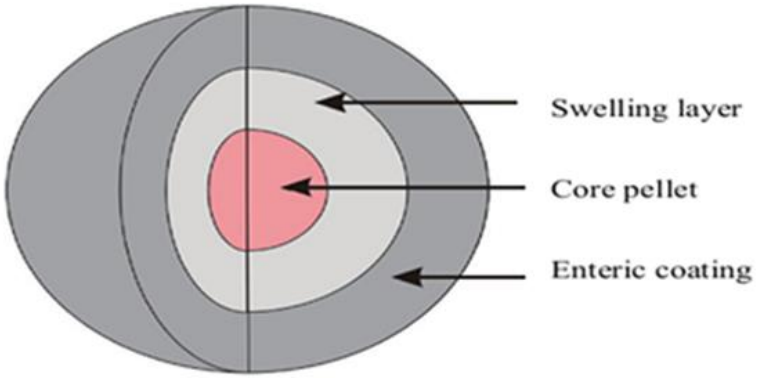
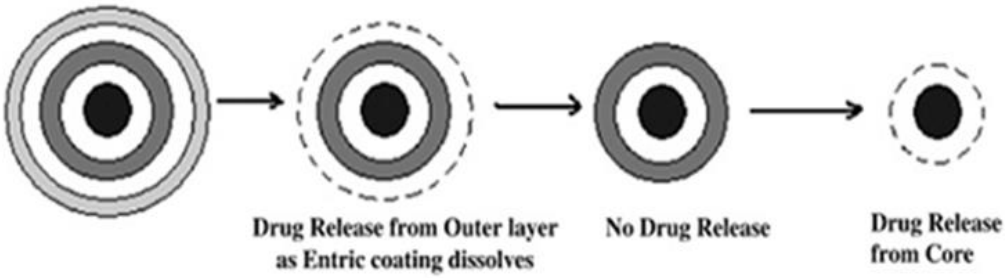
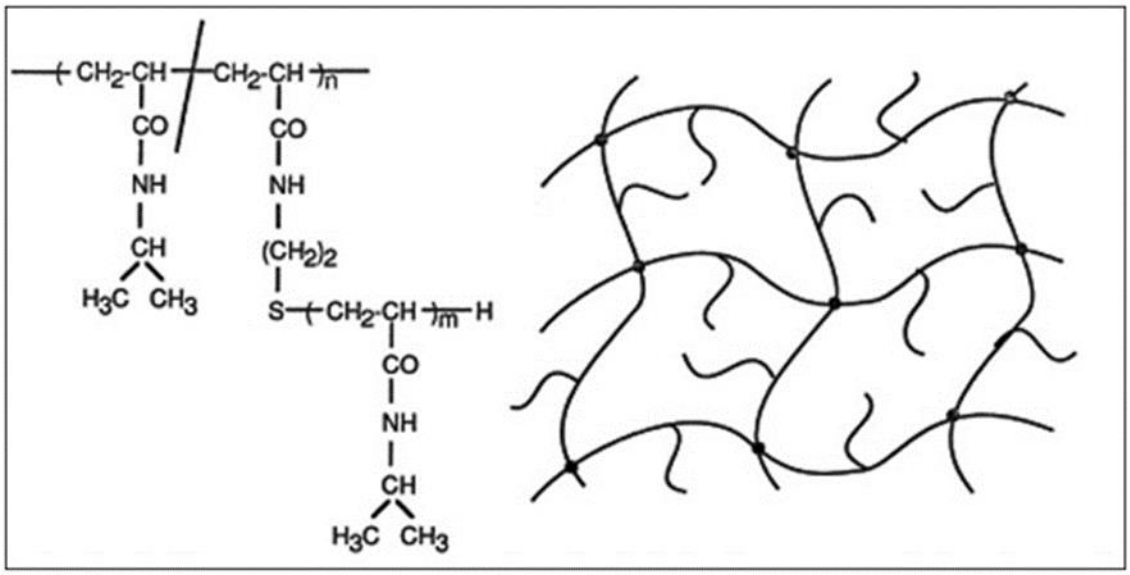


Figure No. 3: Hypothetical design of a multiparticulate pulsatile system



B. **STIMULI INDUCED PULSATILE SYSTEMS:**
I. Temperature induced system
II. Chemically induced System
III. Externally induced System.

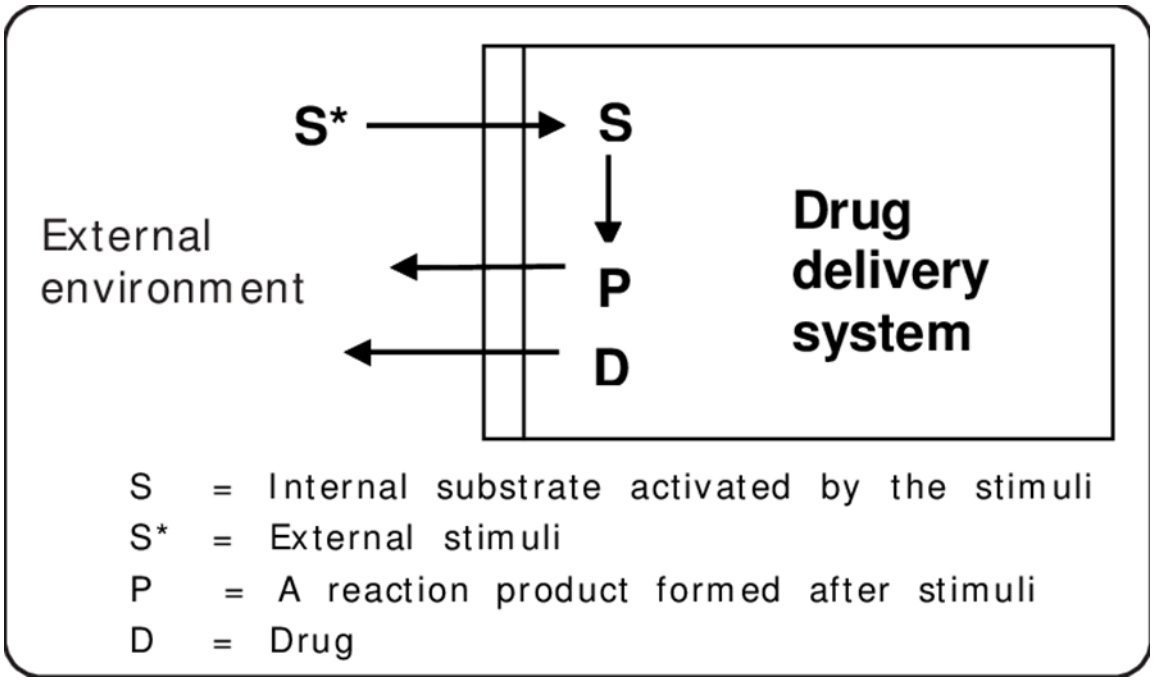
Temperature Induce System: For pulsatile release, thermo-responsive hydrogel systems have been created. The polymer in these systems goes through a swelling or deswelling phase in response to temperature, modulating drug release in the swollen state. Using the reversible swelling capabilities of copolymers of N-isopropylacrylamide and butyryl acrylamide, Y.H. Bae et colleagues created an indomethacin pulsatile release pattern in the temperature ranges of 200C to 300C. To treat cancer, Kataoka et al developed thermosensitive polymeric micelles as drug carriers. End functionalized poly(N-isopropylacrylamide) (PIP Aam) was employed to create the micelle's corona, which demonstrated hydration and dehydration behaviors as temperature was changed.



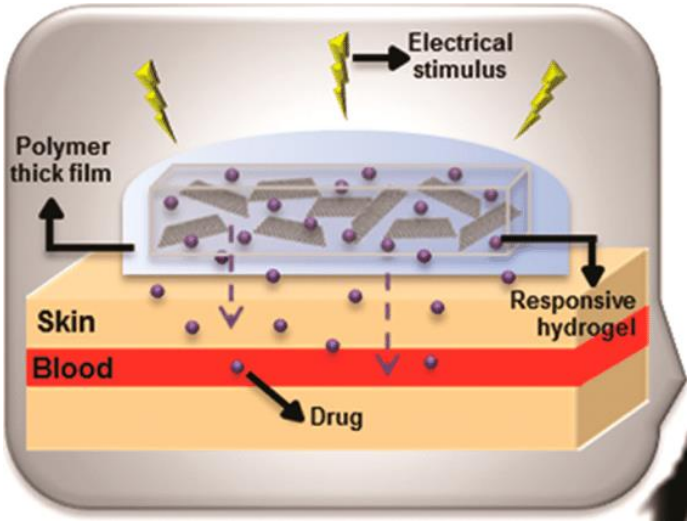
Temperature sensitive pulsatile systems

Chemically Induced System:
The development of stimuli-sensitive delivery systems that release a medicinal substance in the presence of a certain enzyme or protein has piqued attention. The development of a system that can autonomously release insulin in response to rising blood glucose levels is one notable application of this technology. The following are some established ways for glucose responsive medication administration that may be feasible: Ph-dependent systems for glucose-stimulated medication delivery are based on the oxidation of glucose to gluconic acid catalyzed by glucose oxidase. This process can be utilized to cause a pH-dependent membrane to swell. It was decided to create a dual membrane system. Glucose oxidase was immobilized on cross-linked polyacrylamide in the first membrane, which was dubbed the glucose detecting membrane. There are two types of components in a pH sensitive system: one is immediate release and the other is pulsed release, which releases the medicine in reaction to a change in ph. In the case of a pH-dependent system, the fact that distinct pH environments exist at different portions of the gastrointestinal tract has been used. Drug release at a specific place can be achieved by selecting pH dependent polymers.

Externally Stimuli System:
For releasing the drug in a pulsatile manner, another way can be the externally regulated systems in which drug release is programmed by external stimuli like magnetism, ultrasound, electrical effect and irradiation.



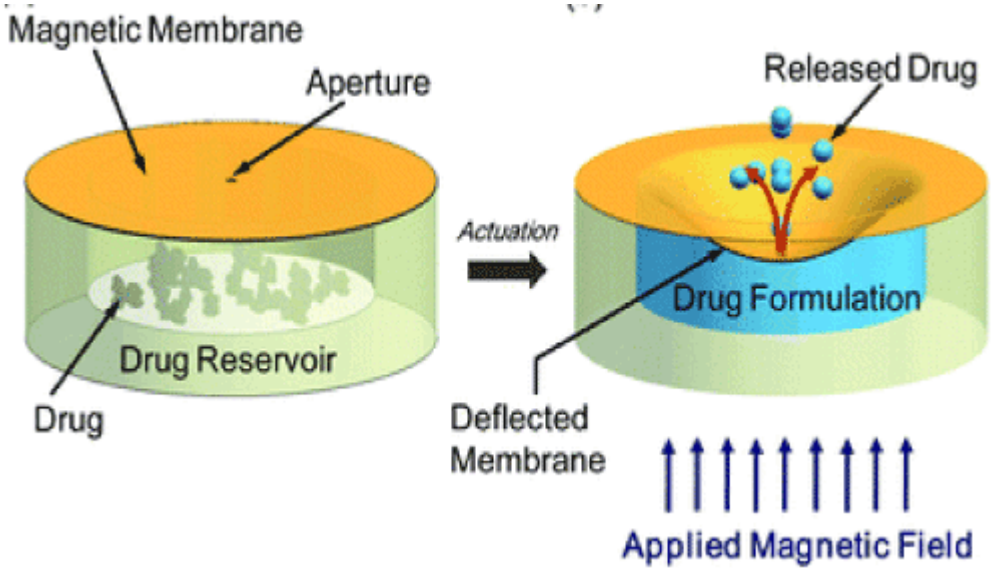
Electro responsive pulsatile release:
An electric field as an external stimulus offers several advantages, including the availability of technology that allows precise control of current magnitude, duration of electric pulses, interval between pulses, and so on.



Ultrasonically stimulated:
Ultrasound is primarily utilized to promote medication absorption across biological barriers such as the skin, lungs, intestinal wall, and blood vessels. Several studies have been published on the impact of ultrasonography on controlled drug delivery.

Magnetically induced pulsatile release:

One of the first approaches to developing an externally controlled drug delivery system was to use an oscillating magnetic to govern drug distribution from a polymer matrix. Magnetic carriers receive a response from included materials such as magnetite, iron, nickel, cobalt, and others in response to a magnetic field.



Medication-release mechanism from the pulsatile drug delivery system:

The drug-release mechanism in PDDS might take the following forms;

Erosion: Some coatings are engineered to dissolve over time, allowing the medicine contained within the particle to be released.

Diffusion: Liquid diffuses into the inside of the sample as molecules come into touch with aqueous liquids in the gastrointestinal tract, and the resulting drug solutions disperse across the release coat to the outside.

Osmosis When water is allowed to enter under the correct conditions, it can build up an osmotic pressure inside the particle.

Need for pulsatile drug delivery system*:*

During the 24 hours, all endogenous biological processes and functions are programmed in time to carry out certain activities at specific times. The pathophysiology of several diseases has predictable circadian rhythms. In order to enhance therapeutic outcomes and reduce adverse effects, in-vivo drug availability can be timed to meet illness rhythms utilizing chronotherapy. When steady medication levels are not desired but a lag phase of no drug release is required, solid oral pulsatile-release dosage forms offer a significant advantage over traditional controlled-release dosage forms.

Asthma is a chronic inflammatory illness of the airways marked by hyperresponsiveness to a wide range of stimuli. Approximately two-thirds of asthmatics have nocturnal asthma symptoms, and the risk of an asthma attack is 100 times higher when sleeping at night than when exercising during the day. If the most appropriate treatment is administered, PDDS has the ability to treat nighttime asthma by releasing drug after a predefined time delay. When the danger of asthmatic episodes is highest, the pulsatile-release dose form can be given before bedtime with a planned commencement of drug release in the early morning hours.

Arthritis is an autoimmune disease that is persistent and inflammatory. Patients with osteoarthritis experience less pain in the morning and more at night, whereas those with rheumatoid arthritis experience pain that peaks in the morning and gradually diminishes throughout the day. The use of NSAIDS for all types of arthritis should be timed so that the highest blood level of the medicine coincides with the peak pain. The plasma concentrations of C-reactive protein and interleukin-6 in rheumatoid arthritis patients have a diurnal cycle. Osteoarthritis patients experience less pain in the morning and increased agony at night. Patients with rheumatoid arthritis experience discomfort that peaks in the morning and gradually fades throughout the day.

Cancer If anticancer medicines are provided while keeping tumor cell cycles in mind, chemotherapy may be more successful and less hazardous. It will be less hazardous to normal tissue this way. During each daily activity phase of the circadian cycle, blood flow to tumors and tumor growth rate are up to three times higher than during the daily rest phase. The concept of chronotherapy has the potential to improve current

cancer treatment options. Chronotherapy, on the other hand, is still uncommon, with just 50 cancer hospitals worldwide using it. During each day activity phase of the circadian cycle, blood flow to tumors and tumor growth rate are up to threefold higher.

Diabetes: Researchers discovered and examined the circadian pattern of glucose and insulin production in diabetics. Following a meal, blood sugar levels rise. The 'Pulsatile drug delivery system' (PDDS), for example, is a new therapeutic in which drug delivery is timed to the circadian rhythm. This technology aids in the delivery of drugs with the fewest possible negative effects.

Cardiovascular Diseases: Angina pectoris, ventricular arrhythmia, acute myocardial infarction, sudden cardiac death, stroke, fatal pulmonary embolism, and hypertensive crisis, as well as other cardiovascular disorders, are all more common in the morning. Cardiovascular events peak between 6 a.m. and 10 p.m. in a diurnally active person. In the morning, capillary resistance and vascular reactivity are higher, and later in the day, they are lower. In the morning, platelet agreeability increases while fibrinolytic activity decreases, resulting in a state of relative hypercoagulability of the blood.

Disease	Chronological behavior	Drugs used
Peptic ulcer	In the afternoon and at night, acid output is at its peak	H2blockers
Cancer	During each daily activity phase of the circadian cycle, blood flow to tumors is three times greater than during the daily rest phase	Vinca alkaloids, Taxanes
Duodenal ulcer	At night, gastric acid secretion is highest, and gastric motility, small bowel motility, and gastric emptying are all slower.	Proton pump inhibitors
Neurological disorders	The behavioral classification of convulsive occurrences and the core pathophysiology of epilepsy	MAO-B inhibitor
Asthma	Attacks are more likely to happen at night or early in the morning	B2 agonist, Antihistamines
Arthritis	The intensity of the pain rises at night	NSAIDs, Glucocorticoids
Cardiovascular diseases	During the sleep cycle, blood pressure is lowest, and it rises rapidly in the early morning.	Nitroglycerin, calcium channel blocker, ACE inhibitors

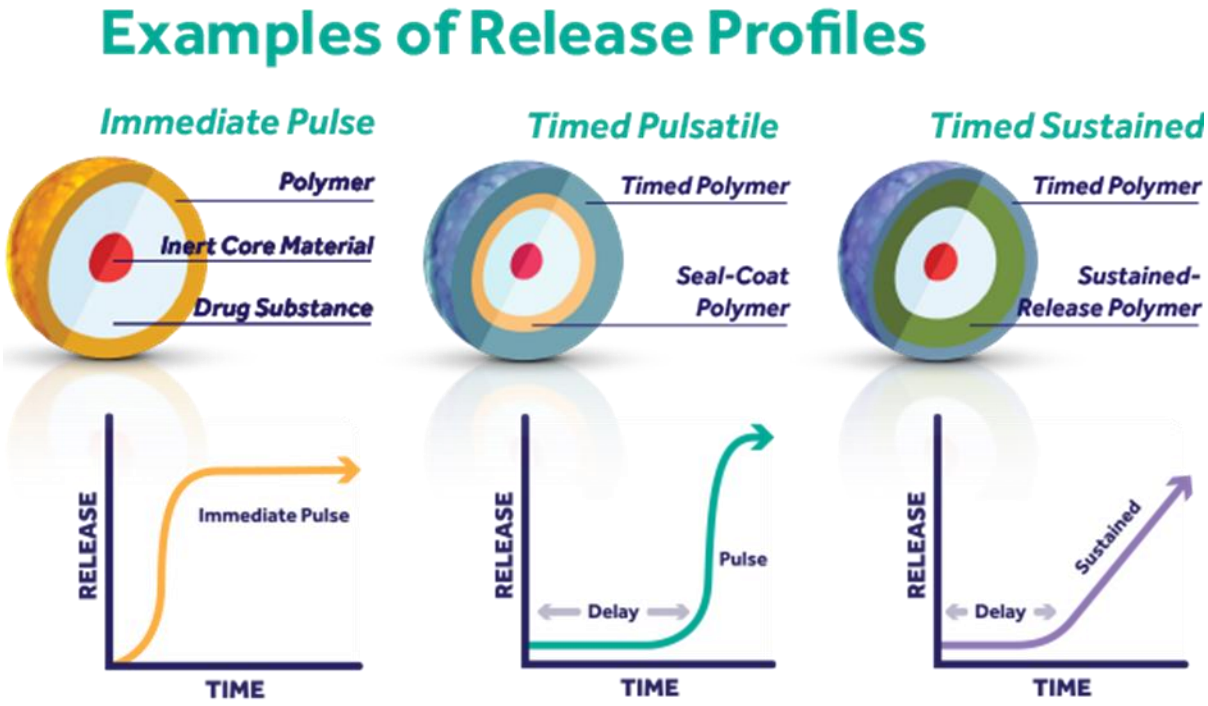
Technologies Used in Chrono pharmaceutics:

The main goal of chrono pharmaceutics is to administer the drug in higher concentrations when it is most needed and lower concentrations when it is least needed in order to reduce needless side effects.

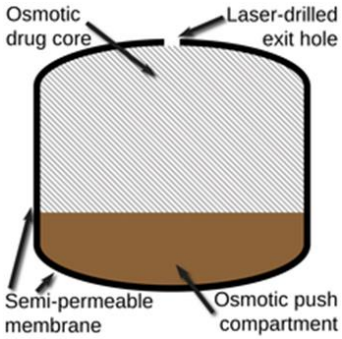
1. DIFFUCAPS® Technology
2. OROS® technology
3. PulsincapTM technology
4. TIMERx® Technology
5. CONTIN Technology
6. GEOCLOCK® Technology
7. Three-dimensional printing®
8. Chrono modulated infusion pumps

1. DIFFUCAPS® Technology: This technique is used to create unit dose forms such as capsules. It is made up of one or more populations of particles that contain drugs (beads pellets, granules etc.). An inert particle or an alkaline buffer crystal could be used as the drug's core. Some drugs' bioavailability or digestion are affected by pH differences in the gastrointestinal tract. This pH sensitivity could present issues, particularly if a continuous or regulated release mechanism is used. Poor particular product ingredients that are insoluble at pH levels higher than five are a major source of concern. Diffucaps technology enables the development and marketing of modern, regulated-release delivery systems for single- or twice-daily doses of single medications and drug formulations with significant pH-dependent soluble profiles or low bioavailability in biological fluids. Diffucaps are multi-particular beads made up of numerous release-controlled

drug sheets, excipients, and polymers. For medicines that are poorly soluble in gastrointestinal pH, pH environments beyond 8.0, or biological liquids, the beads contain a layer of organic acids or alkaline solution that regulates the bioavailability of the drug by producing an optimal pH microenvironment. Because of the versatility of the Diffucaps technology, changing the launch profile and dosage concentration to get the required in vivo outcomes will be simple.

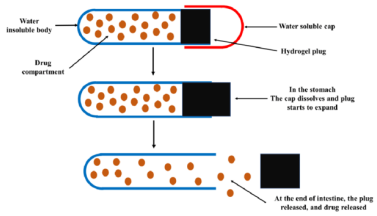


2. <u>OROS® technology</u>: The OROS delivery system has been implemented for medications that are insufficiently soluble in water. A tablet core with a bi-layer or tri-layer including a layer of push and one or more layers of medications makes up the push pull system. Drugs, osmotic agents, and binding agents that are insufficiently soluble make up a medicine surface. Osmotic agents are



used in this technology to deliver preprogrammed, controlled drug administration to the gastrointestinal tract. Covera- HS®, a revolutionary antihypertensive medication, was developed using this technology, particularly the OROS® delayed push pullTM mechanism, commonly known as controlled onset extended release (COER).

3. <u>PulsincapTM technology</u>: The PulsincapTM system is a drug delivery system that encloses a drug formulation in a water insoluble gelatin capsule body shell. The open end of the body is sealed with a swellable plug called a hydrogel plug, which defines the lag time and releases the drug in a pulse (all at once) after the soluble cap



dissolves, followed by erosion or expulsion of the hydrogel plug when it comes into contact with gastric fluid. The lag time is determined by the thickness of the plug and the location where it is inserted.

4. TIMERx® Technology: TIMERx is a pregranulated combination of synergistic heterodisperse polysaccharides (most commonly xanthan gum and locust bean gum) and a saccharide component (generally dextrose). Physicochemical and pharmacokinetic features and release profiles of a wide range of medicines can be accommodated. The material offers consistent packing qualities across a wide range of particle sizes and can be processed into tablets either direct compression or traditional wet granulation. Xanthan gum and locust bean gum are combined with dextrose in this method. In the presence of water, the physical contact between these components results in the formation of a strong binding gel. The rate of water penetration from the GIT regulates medication release.

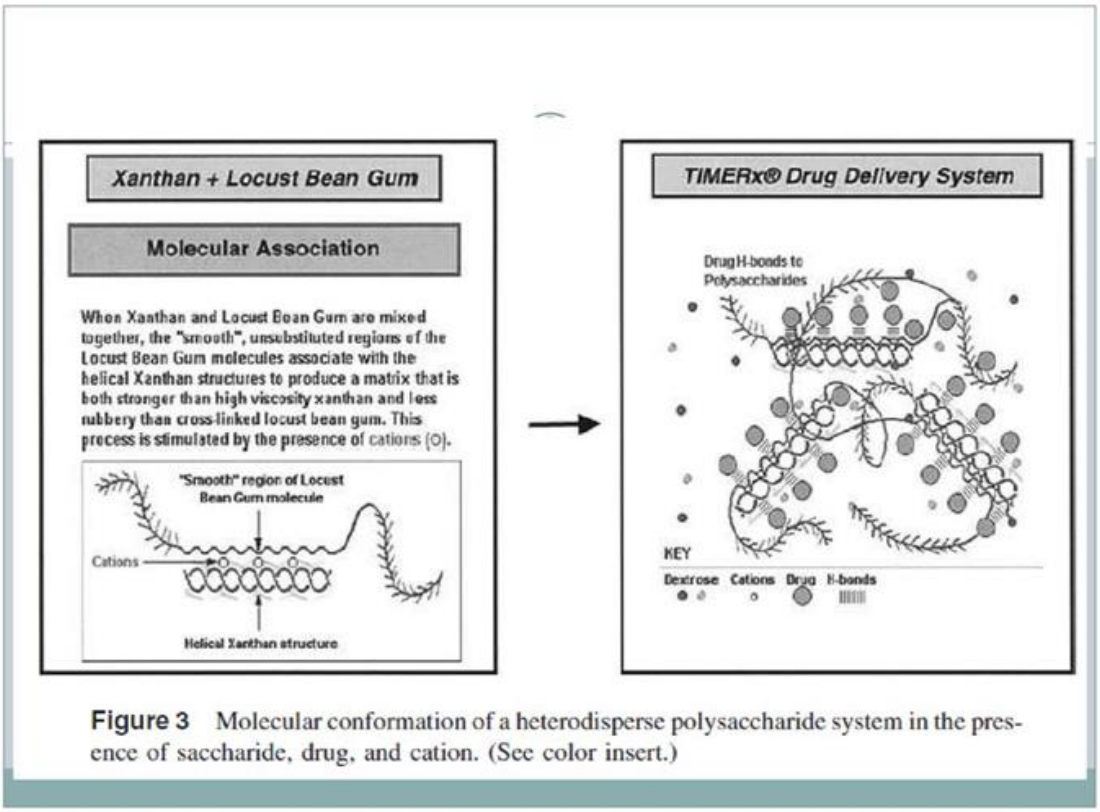
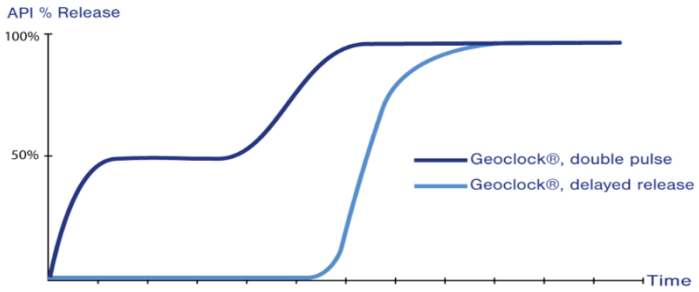


Figure 3 Molecular conformation of a heterodisperse polysaccharide system in the presence of saccharide, drug, and cation. (See color insert.)

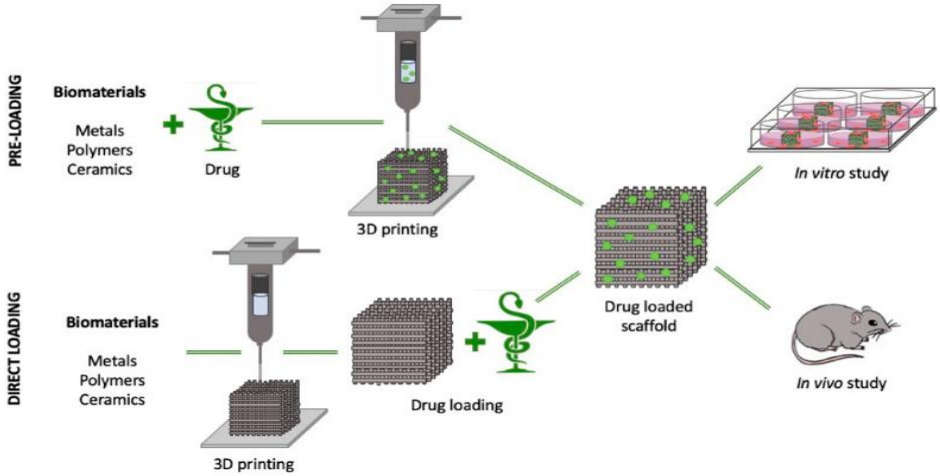
5. CONTIN Technology: The cellulose polymer is solvated using a volatile polar solvent in this method. To produce molecular coordination complexes, the solvated cellulose polymer is counteracted with aliphatic alcohol. Because of its consistent porosity and wide range of applications, the complex is employed as a matrix in controlled release formulations. This method has been used to create long-acting tablets containing aminophylline, theophylline, morphine, and other medicines. API physiochemical modification A proprietary approach is utilized to change the physicochemical properties of the drug, such as solubility, permeability, and partition coefficient. The approach is useful when it has been established that medication solubility and permeability affect bioavailability. Chemical structure, melting point, and molecular weight can all be changed to modify physicochemical properties. This technique has been used to develop a chronotherapeutic system for antihyperlipidemic statins and ant ulcerative medicines.



Geoclock® tablets include an active medication inside an exterior tablet layer made up of a mixture of hydrophobic wax and brittle material.

6. GEOCLOCK® Technology: To provide a pH-independent lag time prior to core drug administration at a specified release rate, Geoclock® tablets include an active medication inside an exterior tablet layer made up of a mixture of hydrophobic wax and brittle material. This dry coating method is designed to allow for the timed release of both slow and fast release active cores by releasing the inside tablet first, then progressively disintegrating the outer shell. LodotraTM, a rheumatoid arthritis medicine developed by Skye Pharma, uses this unique technology to administer the active pharmaceutical ingredient at the most appropriate time of day to treat the disease condition. To provide a pH-independent lag time prior to core drug administration at a specified release rate,

7. Three-dimensional printing®: Three-dimensional printing (3DP) is a rapid prototyping (RP) method. It is a unique solid freeform manufacturing process that has been utilized to the fabrication of sophisticated pharmaceutical medication devices. Prototyping entails using powder processing and liquid binding ingredients to create precise layers. Many advantages of the 3DP system over other procedures in enhancing pharmaceutical applications have been reported in the literature, including innovative ways in the design, development, manufacture, and marketing of various types of solid dosage forms. 3DP was used to create complex oral dose forms that demonstrated lagged release, extended release, double release, and zero-order release. Variable printing parameters were used to alter release



properties such as lag time and release rate. A surface degradation/erosion system based on HPMC was used to create dual-release and zero-order-release forms.

8. Chrono modulated infusion pumps: Melodie®, Programmable synchro med®, Panomat®, V5 infusion, and Rhythmic® pumps are among the infusion pumps available on the market for chrono modulated medication application. The portable pumps are typically light (300-500 g) to allow for easy travel and precise drug delivery. In the case of insulin therapy, an implantable infusion pump with an insulin reservoir is surgically implanted in the left upper or lower quadrant of the abdomen's subcutaneous tissue. Insulin is delivered intraperitoneally via a catheter that runs from the pump through the muscle layers and into the peritoneal cavity, where it floats freely. By introducing a needle through the skin into the pump, this insulin-containing reservoir is replenished once a month or every three months at the physician's office. The patient adjusts the doses within the range established by the physician using radiotelemetry and an electronic device held above the pump. Pumps are utilized in the treatment of ailments such as cancer and diabetes.

Formulation of pulstatile drug delivery system:

METHODS:

Formulation of core tablets by direct compression:
The direct compression method is used to make the inner core tablets. It's a technique that involves mixing and processing formulation materials before compressing them into tablets. The tablets are made from powder API or other excipients directly. The production of tablets utilizing the direct compression method entails three processes. Die feeders, dry binders, and direct compression are the first items on the list.

Formulation of mixed blend for barrier layer:
By using the direct compression method, different compositions were weighed dry mixed for about 10 minutes and utilized as press coating material to make press-coated pulsatile tablets.

Preparation of press-coated tablets:
A dry-coated device is proposed for medication release after a configurable amount of time. It is primarily intended for use in the treatment of disorders that are affected by circadian rhythms. Either gellable or erodible polymers were used in the shell formulations that were evaluated. Uncoated cores and press-coated devices were compared in terms of dissolution profiles. A penetrometer was used to test the gellable and/or erodible characteristics (properties) of the barrier compositions. Until the polymeric shell is entirely degraded or inflated, the coatings restrict medication release from the core. The core composition has no bearing on the initiation of the release; it is solely dependent on the shell formulation. The existence of an erodible barrier has no effect on the release kinetics of the drug contained in the core, except for a temporal lag, however a swellable polymeric shell can be used to vary the release kinetics of the drug contained in the core.

Evaluation of press coated tablets:
Weight variation:
Twenty tablets are chosen at random from each batch and weighed separately. The standard deviation and average weight are computed.

Thickness:
Three tablets are selected from each batch of formulation, and the thicknesses of the tablets are measured using a Vernier calliper. The thickness of the average was calculated.

Hardness:
The Monsanto tablet hardness tester was used to determine the hardness. The average hardness in terms of kg/cm2 was estimated after measuring the hardness of five tablets in each batch.

Friability:
The tablet's friability was tested using the Roche friabilator. In the friabilator, a pre-weighted sample of tablets was put and subjected to 100 rotations. The tablets were reweighed after being dusted with a light muslin towel.

Wetting time:
The contact angle affects the wetting time of the dosage form. In a small Petri dish holding 6 ml of water, a folded piece of tissue paper was inserted twice. The time it took for the tablet to completely moisten the paper was measured.

Disintegration time:
The LABINDIA DT 1000 USP disintegration test device measures the time it takes for RRCTs to disintegrate. One tablet was inserted in each tube and the basket rack was positioned in a 1-liter beaker containing phosphate buffer pH 6.8 at 37°C 1°C such that the tablet remained 2.5 cm below the surface of the liquid to measure the disintegration time. The time

it took for the tablets to completely disintegrate was recorded.

In-vitro release studies:
The tablet was placed in the basket of the LABINDIA TS 8000 USP dissolution test apparatus, which was then set in motion at 50 rpm for 1 hour. At 15-minute intervals, 5 ml of sample was extracted and replaced with pH 7.2 phosphate buffer solutions. The presence of medication was determined using a UV spectrophotometer at 342 nm with a buffer solution as a blank.

In-vitro Dissolution methods:
In-vitro procedures for press-coated tablets The standard paddle method was used to study the dissolution of Pulsatile delivery systems at 37 0.5 °C using 0.5 percent w/v aqueous solution sodium lauryl sulphate in a USP-II dissolution device at 50 rpm. At pre-determined time intervals, 5 ml of filtered aliquot was manually extracted and replaced with 5 ml of fresh 0.5 percent sodium lauryl sulphate solution kept at the same temperature. A UV spectrophotometer was used to evaluate the samples at 342nm. Each formulation's lag time and percentage release were calculated.

Release Kinetics:
The dissolution data was fitted to four popular release models, including zero order, first-order, Higuchi, and Peppa's-Korsemeyer equations, as part of a model-dependent strategy. Zero order or first order kinetics were used to characterise the sequence of drug release from matrix systems. The Higuchi equation and Peppa's-Korsemeyer equation were used to investigate the mechanism of drug release from matrix systems.

zero order release kinetics
$Q = kot$
First order release kinetics
$In (1-Q) = - K1t$
Higuchi equation
$Q=K2t ½$
$Mt/M = K.tn$
Peppa's and Korsemeyer equation (PowerLaw)
Where Q is the amount of drug released at time t,
K0= zero order rate constant, K1= first order rate constant,
K2= Higuchi rate constant,
Mt is the amount of drug released at time t and M is the amount released at time thus,
the Mt/M is the fraction of drug released at time t,
k is the kinetic constant and n is the diffusion exponent.

Stability Studies:
Stability studies of the improved formulation of Atenolol press coated tablets were conducted to investigate the influence of formulation additives on the drug's stability as well as the formulation's physical stability according to ICH guidelines.

CONCLUSION:
The range of systems and approaches that can be used to deliver therapeutics is growing and advancing at an incredible rate, so learning about the advances in drug delivery has important implications for anyone working in health care and related sectors. Currently, Pulsatile drug delivery is gaining cumulative attention as it offers a more sophisticated approach to the traditional sustained drug delivery, a constant amount of drug released per unit time or constant blood levels. Pulsatile drug delivery aims to release drugs on a programmed pattern i.e.: at appropriate time and/or at appropriate site of action.

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