Development of Floating Pulsatile Drug Delivery Systems: Current Scenario and Approaches in Chronotherapeutics

A. Bharathi*, S. Nookaraju
Department of Pharmaceutics, KVSR Siddhartha College of Pharmaceutical Sciences, Vijayawada-10, A.P, India
***Corresponding Author:**Dr. A. Bharathi
Bharathi.arigela004@gmail.com

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ABSTRACT
Floating pulsatile drug delivery systems are gaining popularity because they administer medications in the appropriate place, at the right time, and in the right amount. The floating pulsatile idea is used to improve the stomach residence of a dosage form with a lag phase followed by a burst release. In recent years, numerous methods for chronopharmaceutical drug delivery have been created and thoroughly investigated, including time-controlled, pulsed, trigged, and programmed drug delivery systems. The current review paper focuses on chronotherapy disorders that require chronotherapeutics, pulsatile drug delivery, particularly floating pulsatile drug delivery, and new advancements in this technology.

Keywords: Floating pulsatile drug delivery system, Time-controlled, Chronotherapeutics.

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INTRODUCTION

The major goal of this study was to create a design for a floating pulsatile drug delivery system that would achieve no drug release while floating and pulsed drug release in the distal small intestine. To achieve chronotherapeutic medication release, which is utilised in the treatment of cancer, cardiovascular disease, asthma, osteoarthritis, spondylitis, and other chronic and life-threatening illnesses, to increase patient compliance[1]. Drugs are delivered via the FDDS system at a specified place, in a predetermined amount, and at a predetermined time. Because of their low density relative to the gastric fluid in the stomach, FDDS remain buoyant there for a long time, gently releasing the medication at

the proper rate. The fundamental idea behind the FDDS is straight forward to develop dosage forms with a lower density than the fluid in the stomach. These systems maintain a steady level of drug concentration in the blood plasma. In order to release the dosage form and keep the drug level in the blood plasma constant, the drug typically floats in the stomach fluid and slowly dissolves at a predetermined rate[2].

Chronobiology is an area of science that is described as the study of biological rhythms and their mechanisms over time. "Chrono"

refers to time, while "biology" refers to the study of science or life[3].

Chronopharmacology is the study of how the pharmacological effects of various medications change as the hours of the day change.

Chronotherapy This is a type of medical treatment that involves coordinating biological rhythms.

Biological rhythms A biological rhythm is an internal physiological mechanism that sustains itself. It is described as a process that happens on a regular basis in an organism together with, and frequently as a result of, repeated changes in the environment. Our bodies' rhythms, also referred to as our biological clocks, get their cues from the environment and the solar system's rhythms, which mark the transition from one season to another and turn darkness into day. Our genetic makeup also affects how our internal clocks work. These timepieces affect how our bodies alter throughout the day.

There are 4 types of rhythms in our body:

Ultradian rhythms Oscillation is shorter duration of action are known as ultradian rhythm (more than one cycle per 24 hours) e.g. 90 minute sleep cycle.

Infradian rhythms Oscillation is longer than 24 hours (Less than one cycle per 24 hours) [4].

Seasonal rhythms: such as seasonal affective disorder (SAD), this causes depression in susceptible people during the short days of winter.

Circadian rhythms It is defined as self-sustaining, Endogenous oscillations that occur with a periodicity of about 24 hours. The term circadian is derived from the Latin circa it means- about and dies which can be defined as- a day. Generally Circadian rhythms are synchronized according to internal biologic clocks related to the sleep-wake cycle[5].

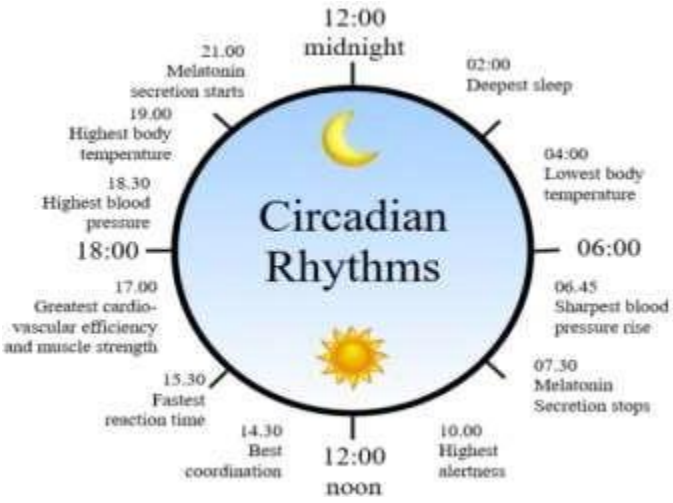


Fig. 1: Circadian Rhythms in Human Body.

Circadian rhythms: The biological rhythm within a single day is termed as circadian rhythm. Here, the oscillation time is 24 hours. Human circadian rhythm is based on the sleep-activity cycle, is influenced by our genetic makeup, and hence affects the body's functions day and night (24-hour period)[6]. The dependence of bodily functions in certain disease states on circadian rhythm is well known. However, chronobiological studies have established circadian rhythm for almost all body functions, e.g., heart rate, blood pressure, body temperature, plasma concentration of various hormones, gastric pH and renal function[7]. It has become apparent that rhythmic processes are indispensable for the treatment of human diseases. Just as physiological functions vary over time, pathological states of disease have circadian rhythms.

Circadian rhythms are controlled by an inherited master clock network consisting of paired suprachiasmatic nuclei (SCN). The discovery of a rhythmic marker for determining dose time will lead to advances in chronopharmacotherapy. To determine the best time of day to administer medications in order to maximise their therapeutic effects and/or minimise their negative effects[8].

Chronotherapeutics: Based on the dosing form, a chronotherapeutic drug delivery system can be divided into two categories: single pulse systems and multiple pulse systems. A single pulse system, which may be the distal portion of the small intestine or the colon, provides the greatest amount of medication to that area of the GIT after a certain lag time. A multiple pulse device delivers the medication in split doses via accompanying pulses, with advantages such as lower dosage, fewer drug-related side effects, and increased patient compliance. According to research, some medications may function better if their administration is timed to coincide with day-night patterns and circadian rhythms. To achieve constant drug levels over the course of a 24-hour period, specific medications are delivered in bursts at circadian timings associated with pathological disorders. This may change the custom of prescribing medications at regular intervals throughout the day[9].

PULSATILE DRUG DELIVERY SYSTEM:

A pulsatile drug delivery system is one that distributes the drug quickly and completely after a lag period, at the correct place, at the right time, and in the right amount, thereby enabling spatial and temporal delivery and boosting patient compliance. These systems are properly planned in accordance with the body's intrinsic rhythm[10].

Need of Pulsatile Drug Delivery System:

Many biological functions have a circadian rhythm, which means that their activity increases or decreases throughout time. A number of hormones, including renin, aldosterone, and cortisol, exhibit daily and timely changes in blood levels. Circadian effects are also seen in stomach pH and acid secretion, gastric emptying, and gastro-intestinal blood transfusion. Circadian rhythm can affect acid secretion, stomach emptying, cholesterol production, and gastrointestinal blood transfusion. Chronopharmacotherapy is used to treat

diseases that exhibit circadian cycles in their pathophysiology, such as bronchial asthma, myocardial infarction, angina pectoris, rheumatoid arthritis, ulcers, and hypertension. Lag time is critical for medications that undergo acidic breakdown (for example, peptide drugs), which irritate the stomach mucosa or cause nausea and vomiting. When a medicine is targeted at distal organs of the gastro-intestinal tract (GIT), such as the colon, drug release should be avoided in the upper two-thirds of the GIT. Drugs go through substantial first-pass metabolism, which is conveniently provided by a pulsatile drug delivery method. Drugs that cause biological tolerance as a result of prolonged drug exposure in the body this technique compensates for lag time [11-13].

Advantages of Floating Pulsatile Drug

- Drugs, such as peptide and protein molecules, can be degraded in the higher gastro-intestinal tract environment.
- It reduces the pharmacological dose while maintaining therapeutic effects.
- The reduction in side effects is substantial.
- Transdermal nitroglycerine, for example, should be avoided due to biological tolerance.
- Improved patient compliance.
- It provides specific targeting site in intestine e.g. colon
- It prevents gastric irritation of drugs.
- It protects the mucosa from certain irritating drugs[14-16].

Disadvantages of Floating Pulsatile Drug Delivery:

- These systems need more amount of fluid in the stomach for drug release to float over a stomach.
- The main issue is a lack of manufacturing reproducibility and efficacy.
- A vast number of process variables are required.
- Higher cost of production is involved.
- To overcome adverse effects, the patient must see a doctor on a regular basis.
- This therapy requires medical care, and regular consultations with sleep specialists are recommended [17-19].

Appropriate Candidates for Floating Pulsatile Drug Delivery Systems:

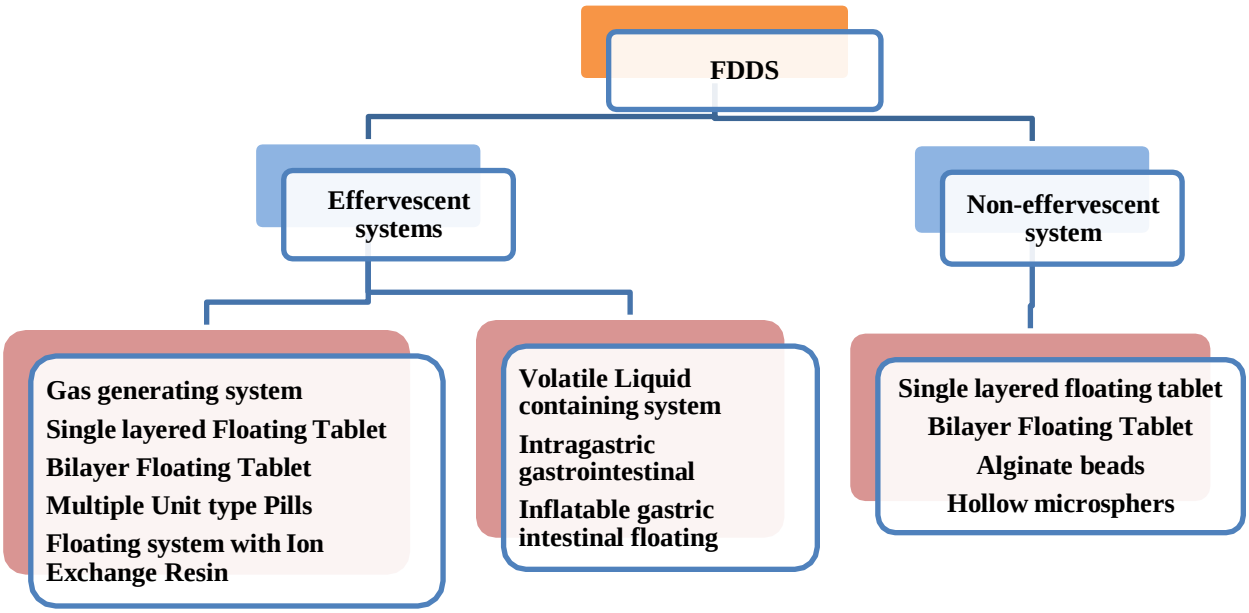
- Drugs with a small absorption window in the GI tract. L-Dopa, Paminobenzoic Acid, Furosemide, and Riboflavin are a few examples.
- Drugs that operate locally in the stomach, for example, misroprostol and antacids
- Drugs those are unstable in the intestinal or colonic environment.
  E.g. Captopril, Ranitidine HCL, Metronidazole.
- Drugs that disrupt the normal microbiome of the colon
  E.g. Antibiotics are used to treat Helicobacter pylori, such as tetracycline, clarithromycin, and amoxicillin.
- Drugs with limited solubility at high PH levels. Diazepam,

chlordiazepoxide, and verapamil are a few examples[20].

Classification of Floating Drug Delivery System:

FDDS can be classified as two types based on the use of formulation variables.

1. Effervescent systems.
2. Non-effervescent systems.



Effervescent Floating Systems:

These are matrix systems made from swellable polymers like methylcellulose and chitosan, as well as other effervescent compounds including sodium bicarbonate, tartaric acid, and citric acid. They are designed in such a way that when they come into contact with the acidic gastric contents, CO2 is released and held in swelling hydrocolloids, which provide buoyancy to the dosage forms.

Non-effervescent Floating Systems:

Gel-forming or swellable cellulose-type hydrocolloids, polysaccharides, and matrix-forming polymers such as polycarbonate, polyacrylate, polymethacrylate, and polystyrene are used in non-effervescent floating dosage forms. The formulation procedure involves thoroughly combining the medication and the gel-forming hydrocolloid. This dosage form swells in contact with gastric juices after oral administration and achieves a bulk density of <1. The air trapped within the expanded matrix gives the dosage form buoyancy.

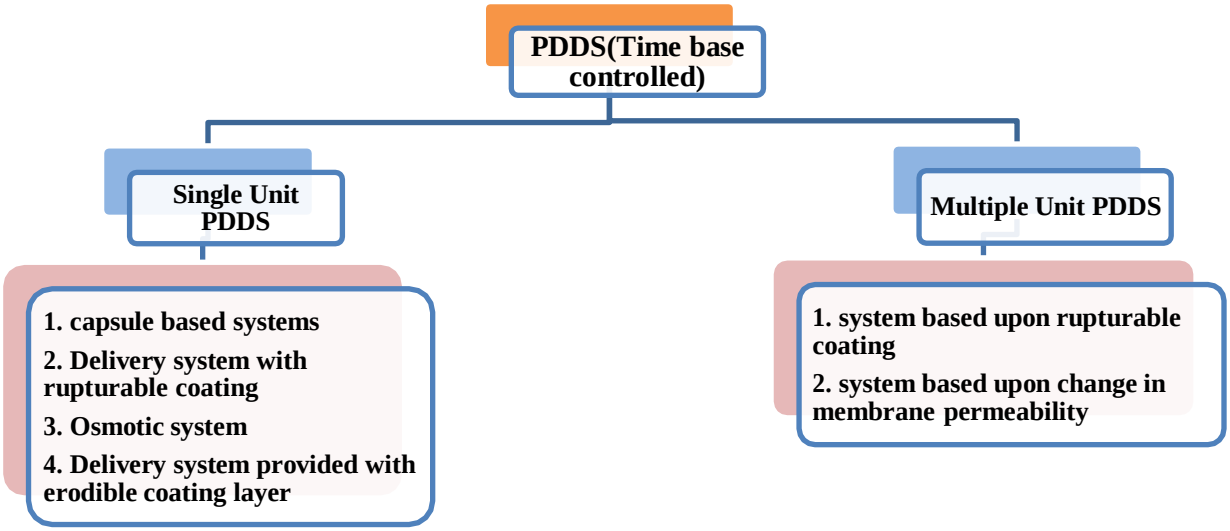
Pulsatile Drug Delivery System Classification:

Pulsatile Drug Delivery Systems are divided into two types.

1. **Single Unit PDDS**
   a. Capsule based systems

b. Delivery system with rupturable coating
c. Osmotic system
d. Delivery system provided with erodible coating layer

2. Multiple Unit PDDS
a. System based upon rupturable coating
b. System based upon change in membrane permeability



1. Single Unit PDDS:

Capsule based systems

Single-unit systems are typically designed as capsules. A plug controls the lag time, which is pushed away by a plug, swelling, or erosion, and the medicine is released as a "pulse" from the insoluble capsule body. To seal the drug contents into the capsule body, a swellable hydrogel stopper was used. When the capsule comes into contact with dissolving fluid or stomach fluid, the plug expands and, after a little delay, pulls itself outside the capsule, releasing the medicine swiftly. This formulation causes no GI irritation and is protected by an enteric coating.

Delivery system with rupturable coating

These systems are built around a reservoir system that has been coated with a rupturable layer or membrane. The pressure created by effervescent substances or swelling agents causes the outer membrane to break.

Osmotic system

Therapeutic system research laboratory Ann Arbour, Michigan, USA, developed the Port system, which consists of a capsule coated with a semi-permeable membrane. Capsule-insoluble osmotically active agent and medication formulation plug.[21] As soon as the capsule made contact with the dissolution fluid, the semi-permeable membrane allowed water to enter, pressure to build up, and the insoluble plug to be released after a delay. A similar technique was used to distribute methylphenidate.

Delivery system provided with erodible coating layer

The drug reservoir in this system is surrounded by a soluble barrier layer that dissolves over time, and the drug is released all at once after this lag time. A hydrophilic polymer, HPMC coats a core carrying a drug reservoir in a chronotropic system.[22-24] The thickness and viscosity grade of HPMC determine the lag time and the commencement of action. The time clock system is a solid dosage form coated with an aqueous dispersion delivery mechanism.[25] This coating consists of a hydrophobic surfactant layer to which a water-soluble polymer has been added to promote adherence to the core.

Multiple Unit PDDS

System based upon rupturable coating

Individual units are coated with effervescent or swelling chemicals to achieve the rupturing effect. Bai et al. developed a pulsatile drug delivery system made up of a number of particles split into discrete delivery units, each with its own unique makeup. The breach of the membrane restricted drug delivery. To produce pulsed release, the thickness of the coating and the amount of water-soluble polymer were adjusted. Individual particles have the same internal core composition. The thickness of the external coating layer, on the other hand, varied.[26]

System based upon change in membrane permeability

A sigmoid release system (SRS) based on the interaction of acrylic polymers with quaternary ammonium groups in the presence of various counter ions is described. SRS systems are made up of pellet cores that have been coated with ammonio-methacrylate copolymer USP / NF type (B). The medium's water dissolves succinic acid. The medication and acid solution inside improve the permeability of the polymer sheet. This technology was used to create an acidic core.

Diseases are required Floating Pulsatile Drug Delivery with Chronotherapy: [27-29, 30-32]

Disease	Chronobiological Behaviour	Drugs Used
Asthma	Precipitation of attacks during the night or early morning	Antihistamines, B2 agonist
Cancer	During each daily activity phase of the circadian cycle, blood flow to the tumor is three times greater than during the daily rest phase.	Vinca alkaloids, taxans
Cardiovascular disease	Blood pressure is at its highest during the sleep cycle	Nitro-glycerine, CCBs, and ACE inhibitors
Diabetes mellitus	Increase in blood sugar level after a meal	Sulfonylurea, Insulin
Duodenal ulcer	Acid secretion is high in afternoon and at night	H2 blockers
Arthritis	Inflammatory cytokines, such	NSAIDS, Glucocorticoids

	as interleukin-6, are released in large amounts in the early morning, which causes pain to increase.	

CHRONOTHERAPY IS NEEDED FOR DISEASES:

The following some diseases are needed chronotherapy. They are

1. Bronchial asthma
2. Cancer
3. Hypertension
4. Diabetes
5. Arthritis
6. Alzheimer's disease
7. Parkinson's disease

Bronchial asthma:

It is distinguished by airway inflammation, which causes hyper responsiveness of the lower respiratory tract to a variety of environmental stimuli.[33] In asthmatic patients, airway resistance gradually increases at night. This type of asthma is known as nocturnal asthma. It is an asthma exacerbation characterized by an increase in symptoms, airway reactivity, and/or lung function.[34] The bulk of bronchospastic events occur between 2 and 6 a.m. every day.[35] The agents are programmed to release the active medication during the attack. i) In one trial, a time-release formulation of theophylline (Theo-24) attained therapeutic drug concentrations at night while avoiding dangerous levels during the day when the dose was consumed at 3 p.m. [36] ii) A single daily inhalation corticosteroid dosage.

Cancer:

Many clock genes are involved in the transcriptional and post-transcriptional activation and inhibition of regulatory loops in mammalian cells that create circadian oscillation.[37] CLOCK: BMAL1 or NPAS2:BMAL1 protein dimers are often responsible for activating clock gene transcription per and cry. Clock-gene-related rhythm changes at the tissue level may be observed as a result of the resynchronization of individual cancer cells that form a solid tumour. Another set of researchers evaluated the effect of continuous infusion of 5-fluorouracil (5-FU) with circadian patterns of 5-FU administration that exhibit peaks at 4 a.m., 10 a.m., 4 p.m., or 10 p.m.[38-39] According to the findings, the cytotoxic effect of 5 FU is minimal for circadian administration.

Hypertension:

One billion individuals worldwide suffer from hypertension, which is a chronic condition. According to physiological factors associated with early morning emergence, post-awakening occurs between 4 and 8 hours after awakening and is marked by an increase in systolic and diastolic blood pressure of up to 3 mmHg/hour.[40] Walking in the morning raises blood pressure and heart rate, which then start to fall in the afternoon and ultimately achieve systolic and diastolic pressure at night.[41]

Diabetes:

Diabetes results in circadian fluctuations in insulin and glucose. The purpose of insulin therapy is to emulate the physiological rhythm of continuous basal and meal-

stimulated endogenous insulin production in healthy individuals. Patients with diabetes who receive exogenous basal insulin are prevented from producing glucose in the liver.[42,43]

Duodenal ulcer:

In duodenal ulcer patients, stomach acid secretion often peaks in the evening and declines in the morning.[44] While stomach perforations exhibited a primary peak about noon and a secondary peak close to midnight, duodenal perforations showed the highest incidence in the afternoon.

Arthritis: Rheumatoid arthritis and osteoarthritis are the two types of arthritis pain that have been documented. Arthritis is dependent on chronobiology patterns. The morning is always the worst for rheumatoid arthritis symptoms, although long-acting NSAIDs demonstrated the best therapeutic results at bedtime and reduced side effects.[45] Osteoarthritis tends to hurt more in the morning and lessen in the evening. If taken at least 4 to 6 hours prior to the pain's peak, ibuprofen may be more helpful at relieving it. Patients with arthritis who take an NSAID before bed experience less discomfort in the morning[46].

Alzheimer's disease:

Patients with Alzheimer's disease also exhibit a disruption in circadian rhythm. Patients with this disease also have increased core body temperatures, irregular circadian rhythms, and deteriorating cognitive and functional abilities[47]. Patients with this illness also have higher core body temperatures. In this condition, circadian irregularities are observed alongside cognitive and functional decline. No other changes have been examined[48].

Parkinson's disease:

Postprandial hypotension and magnified diurnal blood pressure variability are both symptoms of Parkinson's disease and are brought on by autonomic dysfunction[49]. However, due to the difficulty in estimating the daily oscillations in the motor activity pattern of the disease phase and the subsequent effect of medications, the existence of a circadian rhythm in this condition has not been tested in clinical data.

CURRENTLY AVAILABLE DIFFERENT MARKETED PULSATILE DRUG DELIVERY TECHNOLOGIES:

SODAS Technology: Spherical Oral Drug Absorption System (SODAS Technology) Elan's multiparticulate medication delivery technology is called SODA. [18] The SODAS technology, which is based on the creation of controlled release beads, is distinguished by its inherent flexibility, which enables the production of specialized dosage forms that directly address the requirements of various drug candidates[50].

Time Control Explosion System (TCES): For the water-insoluble drug, it is helpful. This invention primarily relates to drug delivery systems for regulated absorption, and more specifically, it combines coating dissolution and explosion mechanisms in coated drug-containing pellets for guaranteed timely release of pharmaceuticals for oral administration. A water-permeable membrane surrounds the core portion, preventing the release of the medicine into the environment[51].

IPDAS Technology: with GI-irritating chemicals, the IPDAS is a high-density multiparticulate tablet technology. IPDAS was first created as a part of the process for creating Elan's exclusive naproxen formulation, Naprelan. The goal was to create a once-daily controlled release method that would function quickly and cause less stomach irritation. Numerous high-density controlled-release beads that are crushed into tablets make up the IPDAS technology. After being swallowed, an IPDAS tablet quickly breaks down and releases drug beads into the stomach.[52]

(OSDrC) Technology: One-Step Dry Coating (OSDrC) Technology Thanks to OSDrC technology, a new era in the manufacture of pharmaceutical tablets is now conceivable. "Unique," "high quality," "low cost," and "innovative" are buzzwords in this new society. The OSDrC rotary tabletting machine's customizable double-punch structure enables the production of medicinal products in a single step. In addition to the mass production of conventional cored (tablet-within-a-tablet) tablets on a commercial scale, this machine is ideal for creating a variety of high-quality pharmaceutical items at an affordable price[53].

Geomatrix technology: The Geomatrix technology can simultaneously release two separate medications at two different rates from a single tablet and can be used to achieve customised amounts of controlled release of specific drugs. It is possible to create a multilayered tablet with a controlled release by using two fundamental core elements: 1) Polymers that are hydrophilic, such as hydroxypropyl methylcellulose (HPMC) 2) Barrier layers that govern surfaces Barrier layers regulate the active-loaded core surface that is accessible for medication release when exposed to fluid.

CODAS Technology: A situation where drug release may be timed to happen after a significant delay after administration is called chronotherapy. To achieve this extended period, Elan created the CODAS Technology (Chronotherapeutic Oral Drug Absorption System). The medicine can be released with a specified delay thanks to Elan's flexible drug delivery technology. The drug release profile produced by the CODAS drug delivery system more closely matches circadian cycles because it allows for a delayed start to drug release [54-55].

PRODAS Technology (Programmable Oral Drug Absorption System): An innovative multiparticulate technology called PRODAS combines the advantages of tableting technology inside a capsule. Several minitablets packaged in a firm gelatin capsule make up the PRODAS delivery mechanism. The PRODAS technology, which is very adaptable, can be used to pre-programme the release rate of a medicine. It is also possible to use minitablets of various sizes to enable increased medication loading[56].

TMDS Technology (Time Multiple Action Delivery system): Multiple ingredient release rates for a single tablet using TMDS technology are controlled and timed. With the aid of TMDS technology, numerous active ingredients can be included in a single tablet formulation to deliver various release profiles over a lengthy period of time[57].

DMDS Technology (Dividable Multiple Action Delivery System): The greater dosage flexibility offered by DMDS enhances product effectiveness while minimising negative effects. When a traditional controlled-release pill breaks, the controlled-release mechanism of delivery frequently disappears. However, DMDS technology enables the tablet to be divided in half, with each piece achieving the exact same release profile as the entire tablet[58].

PMDS Technology (Programmed Multiple-action Delivery System): Comparatively to conventional controlled release technologies, PMDS technology is intended to enable the multiphasic distribution of any active component in a more controlled manner. With the help of our PMDS technology, the active ingredient may be consistently being released at the desired levels and at predetermined intervals.

TIMERx Technology: Essentially, this method blends dextrose, xanthan, and locust bean gums. In the presence of water, these elements physically combine to create a solid, binding gel. The rate at which water enters the TIMERx gum matrix from the gastrointestinal tract determines how quickly the medicine is released. As the water expands to create a gel, the drug is then released.

PULSYS Technology: The PULSYS dosage form is a compressed tablet with pellets inside that are intended to pulsatile release medication at various locations in the gastro-intestinal tract. The dosage form consists of a variety of pellet types with different release characteristics that are mixed in a ratio to induce a steady rise in plasma drug levels early in the dosing period. In comparison to tablet matrix forms, the transit qualities of pellets improve the bioavailability and broaden the overall absorption time window. [59-60]

CONCLUSION:

The most prevalent, preferred, and oldest mode of drug delivery is oral drug administration. In most diseases with biological cycles, sustained and controlled-release drugs are insufficient to have the required therapeutic effect. New delivery methods or techniques that can aid patients therapeutically are constantly needed. One such system is floating pulsatile drug delivery, which uses floating concepts to release the medication at the right time, right place, and right dosage. It is intended for the chronotherapy of diseases and holds great promise for the benefit of patients with chronic diseases like arthritis, cancer, asthma, hypertension, peptic ulcers, and duodenal ulcers. To find the best technology in the world for circadian rhythm discovery, numerous studies on pulsatile medication delivery are being conducted. Due to its distinct characteristics, such as a low probability of dose dumping and patient compliance, this delivery method will likely become the standard method for administering therapeutic drugs in the future.

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