

A Review of Floating Pulsatile Drug Delivery System

¹Pathi Sandeep Kumar, ²S. Rajashekhar, ³Dr. Subrahmaniam Sharma Gontu, ⁴Dr. T.Rama Rao

¹B. Pharm (M. Pharm), ²M. Pharm (Ph. D), ³M. Pharm, Ph. D, ⁴M. Pharm, Ph. D

¹Department of Pharmaceutics,

¹CMR College of Pharmacy, Kandlakoya, Medchal, Telangana, India

Abstract— Oral route of drug delivery is frequently recommended by both healthcare professionals and physicians. It has been suggested that the biological rhythm of the body (circadian rhythm) influences the normal physiological and biological functions, this led to the discovery of the Floating Pulsatile Drug Delivery System (FPDDS). In this method the drugs are released at a localized area at a specific time. As they have lower bulk density than gastric fluid they float in the stomach for longer time periods. In this review we highlight the types of FPDDS, the advantages of this delivery system over other delivery system and the possible disadvantages of this system and how they can be overcome.

Index Terms— Pulsatile Drug delivery, Circadian rhythm, Floating Pulsatile Drug Delivery System (FPDDS), Biological and physiological functions. (*Key words*)

I. INTRODUCTION (HEADING 1)

This research's primary objective is to develop a design for a floating pulsatile drug delivery system that enables no drug release during floating and pulsed drug release in the proximal small intestine. The oral route is likely the most recommended by both patients and healthcare professionals among the numerous drug delivery routes. Time and site-specific modified release dosage forms, also known as programmed release dosage forms or pulsatile release dosage forms, are getting prominence in the oral route. Recent studies suggest that the body's biological rhythm can influence normal physiological functions such as gastrointestinal motility, gastric acid secretion, gastrointestinal blood flow, renal blood flow, hepatic blood flow, urinary pH, cardiac output, drug-protein binding, and liver enzymatic activity, as well as biological functions like heart rate, blood pressure, body temperature, blood plasma concentration, intraocular pressure, stroke volume, and platelet aggregation.

Floating Pulsatile Drug Delivery System is a method in which drugs are released at a localized area and act at a specific time. Because floating drug delivery systems have a lower bulk density than gastric fluid, they stay buoyant in the stomach for longer periods, slowly releasing the medicine at the desired rate. Floating drug delivery systems (FDDS) are a method of retaining medicine in the stomach. They are particularly beneficial for poorly soluble or unstable drugs in intestinal fluids. The underlying principle is to reduce the density of the dose form. Even though the therapeutic dose does not disintegrate, the underlying concept was to maintain a consistent quantity of drugs in the blood plasma. Pulsatile drug delivery systems are increasing enormously in the pharmaceutical industry because they aid with quick drug release at a specific place after a pre-determined off-release interval (lag time) that corresponds to the circadian cycle and enhances patient compliance. Third-generation DDSs, which have a time-controlled function, are being used in the development of new and improved disease therapies. Biological rhythms can be applied to pharmacotherapy while using a dosage form that synchronizes drug concentrations with disease activity patterns.

II. PULSATILE DRUG DELIVERY SYSTEM

After a programmable lag phase, a pulsatile drug delivery system releases medicine in a quick and burst way within a short period. There are multiple circumstances in which medicine must be released instantly (after the delayed film layer ruptures) at a precise location. As a result, these circumstances necessitate the development of delayed quick release systems. This can be customized to the disease's physiology as well as the features of the medication molecule. The pulsed or transitory release of bioactive chemicals at a specified time and site regulates various physiological systems in the body, including metabolism, sleep patterns, and heart attacks. As a result, to simulate the function of a living system, a pulsed release of a certain amount of bioactive chemicals at a predetermined interval is required. As an outcome, the release pattern of such drug administration is circadian. Some drugs are effectively released in pulses. A single dosage form delivered an initial dose of the drug, followed by one release-free interval, then the second dose of the drug, followed by another release-free interval and drug release pulses. A primary goal in medication delivery is to be able to deliver a bioactive molecule and therapeutic agent to a patient in a pulsatile release profile. Because the release is independent of the environment, this method is often known as a time-controlled system.

III. FLOATING DRUG DELIVERY SYSTEM

Floating systems are low-density systems with enough buoyancy to float above gastric contents and stay in the stomach for an extended period. The medicine is delivered slowly at the desired rate while the system floats over the gastric contents, resulting in increased gastro-retention time and fewer fluctuations. Several drug delivery techniques with extended gastric retention duration have been investigated to solve this physiological limitation. Efforts are being made to develop a controlled drug delivery system that can maintain therapeutically effective plasma drug concentration levels for longer periods, reducing dosing frequency and minimizing fluctuations in plasma drug concentration at a steady state by delivering the drug in a controlled and predictive manner. Gastro retentive systems can persist in the gastric region for several hours, considerably increasing the drug's gastric residence duration.

Cohesion, flotation, sedimentation, expansion, altered shape systems, or the administration of pharmacological drugs that delay stomach emptying can all be used to accomplish controlled gastric retention of solid dosage forms. Based on these approaches, floating drug delivery systems appear to be the most promising delivery systems for controlling medication release.

The following are the primary requirements for a floating drug delivery system:

- It should have a specific gravity that is lower than the amount of stomach content.
- It should produce a gel barrier that is cohesive.
- To serve as a reservoir, it must gradually discharge fluids.
- It should gently release contents to act as a reservoir
- It must have a specific gravity lower than the contents of the stomach (1.004–1.01 gm/cm³).
- It must form a cohesive gel barrier.

IV. CHRONOPHARMACEUTICS:

The term "Chrono" is defined as every metabolic event undergoing rhythmic changes in time. According to the researchers, chronotherapeutics is a treatment strategy in which in vivo drug availability is timed to match disease rhythms to enhance therapeutic outcomes and reduce side effects. It is based on the finding that the peak-to-trough rhythmic activity in disease symptoms and risk factors, pharmacologic sensitivity, and pharmacokinetics of many medications are all interrelated.

CHRONOBIOLOGY

Chronobiology is a branch of science that studies the biological mechanisms of disease over time. Biology refers to the study, science, or life, while Chrono refers to time.

CHRONOPHARMACOLOGY

It is the study of the varied pharmacological effects of diverse medications throughout time.

CHRONOTHERAPY

It is a treatment that combines rhythms and medicinal treatment.

BIOLOGICAL RHYTHMS

- **Circadian rhythms** - The 24-hour cycle, which encompasses physiological and behavioral rhythms such as sleeping.
- **Ultradian rhythms** - Biological rhythms that have a shorter period and occur more frequently than circadian rhythms.
- **Infradian rhythms** - These biological rhythms that continue longer than 24 hours.

APPROPRIATE DRUG CANDIDATES FOR FPDDS

1) Drugs with a narrow absorption window in the Gastrointestinal system.

Eg: L-Dopa, Paminobenzoic Acid, Furosemide, and Riboflavin

2) Drugs that have a local effect on the stomach.

Eg: Antacids, Misoprostol.

3) Drugs that are unstable in the gastrointestinal or colonic environment.

Eg: Captopril, Ranitidine HCl, and Metronidazole.

4) Drugs that disrupt the natural microbes in the colon.

Eg: Antibiotics used to eradicate *Helicobacter pylori*, such as Tetracycline, Clarithromycin, and Amoxicillin.

5) Drugs with a low solubility when the pH is high.

Eg: Diazepam, chlordiazepoxide, and verapamil.

ADVANTAGES:

- It avoids first-pass metabolism, which includes protein and peptide metabolism.
- It lowers the drug's dose while maintaining therapeutic effects.
- It is beneficial in the case of drugs with a short half-life.
- Useful for daytime or nighttime activities.
- Drugs, such as peptides and protein molecules, can be degraded in a higher GI tract environment.
- Allows for site-specific release for disease therapy on a local level.
- There is a significant ratio of decreases in side effects.
- Viscosity of lumen contents, as well as GI tract agitation rate.
- It offers a precisely targeted site in the bowel, such as the colon.
- Due to fewer cytochrome p450 isoenzymes, medication interaction is reduced.
- Changes in the pH of the gastrointestinal system do not affect drug release.
- Viscosity of lumen contents, as well as GI tract agitation rate
- Biological tolerance (transdermal nitroglycerin).
- Reduces the impact of food.

DISADVANTAGES:

- A significant number of process variables are required.
- Sometimes a person undergoing therapy will feel extremely hot or cold.
- Incorporates the batch manufacturing procedure.
- Floating systems are ineffective for medications that have an issue with solubility or stability in the gastrointestinal tract.
- A higher production cost is involved.
- The main issue is a lack of manufacturing reproducibility and efficacy.

- This technique can only be used for medications that are widely absorbed throughout the gastrointestinal tract and suffer significant first-pass metabolism.
- The person must keep himself awake until the next sleep schedule, thus he must occupy himself to stay awake till the next schedule.

V. CLASSIFICATION OF PULSATILE DRUG DELIVERY SYSTEM:

1. Time controlled pulsatile drug delivery

A. SINGLE UNIT PULSATILE SYSTEM:

a) System based on capsules

Pulsin cap system Single-unit systems are the most common. The drug is released once the lag time is controlled by a plug that gets pushed away by swelling or erosion. Pulsin cap is a technology that consists of a water-insoluble capsule containing the drug reservoir, designed by R. P. Scherer International Corporation in Michigan, United States. When this capsule comes into touch with the dissolution fluid, it thickens, and the plug pushes itself outside the capsule after a short delay, releasing the medicine quickly. By adjusting the plug's dimension and position, the lag time can be adjusted.

The following polymers were utilized to create the hydrogel plug.

- Polymers that are insoluble but permeable and swellable (e.g., polymethacrylates)
- Compressed erodible polymers (e.g., hydroxypropyl methylcellulose, polyvinyl alcohol, Polyethylene oxide)
- Melted polymers that have congealed (e.g., saturated polyglycolated glycerides, glyceryl monooleate)
- Erodible polymer with enzymatic control (e.g., pectin).
- The Pulsin cap TM device is made up of an impermeable capsule body that contains the medicine and is sealed with a hydrogel plug.
- This plug swells in GI fluid and exits away, delivering medication after a predetermined lag time controlled by hydrogel plug thickness.
- An erodible alternative to the Pulsin cap plug is available.

b. Osmotic system

PORT SYSTEMS:

A gelatin capsule coated with a semipermeable membrane (e.g., cellulose acetate) that contains an insoluble plug (e.g., lipidic) and an osmotically active material, as well as the pharmaceutical formulation, makes up the osmotic system. Water diffuses through the semipermeable membrane when it comes into touch with the aqueous medium, generating an increase in inner tension that discharges the plug after a delay. The thickness of the semipermeable barrier determines the time lag. An osmotically driven capsular system was designed to distribute liquid pharmaceuticals. When the barrier layer is dissolved, liquid medicine is absorbed by highly porous particles, and the drug is discharged via an opening in a semipermeable capsule supported by an expanding osmotic layer.

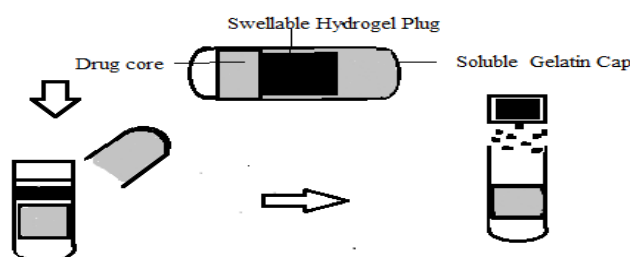


Figure 1: System based on expandable orifice

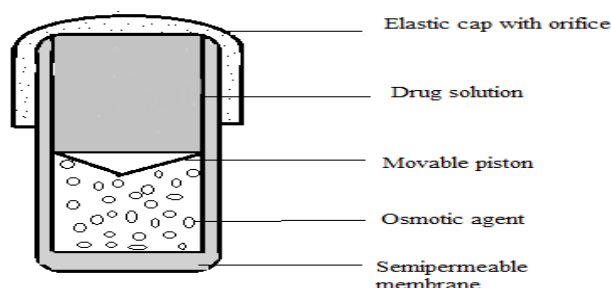


Figure 2: Pulsin cap design system

c. Delivery by a Series of Stops

This system is designed for capsules that can be implanted. The therapeutically active agent and the water absorptive osmotic engine are separated by a slider partition in the osmotically powered delivery capsule, allowing the medicine to be delivered in a pulsatile manner through the aperture. A series of stops positioned along the inner wall of the capsule hinder its movement, creating the lag time required for pulsatile distribution. The partition is compelled to distribute the next batch of medicine as the hydrostatic pressure climbs above the threshold level. The number of intervals and their location along the longitudinal axis determine the pulse intensity.

B. MULTIPLE/MULTI PARTICULATE UNIT SYSTEM:

a. System based upon change in membrane permeability

The presence of different counterions in the medium can affect the permeability and water uptake of acrylic polymers containing quaternary ammonium groups. Based on this ion exchange, several delivery techniques have been created. The polymer of choice for this application is Eudragit. The polymer side chain usually comprises a positively polarised quaternary ammonium group, which is invariably followed by negative HCl counter-ions. Because the ammonium group is hydrophilic, it helps the polymer interact with water, modifying its permeability and allowing water to pass through the active core in a controlled manner. This characteristic is necessary for achieving an accurate lag time. Theophylline was used as a model medication, and sodium acetate was used to make the cores. Eudragit (10% to 40% weight gain) was used to coat these pellets in four distinct layer thicknesses. A link was observed between film thickness and lag time. Even a tiny amount of sodium acetate in the pellet core was discovered to have a significant impact on the drug permeability of the Eudragit film. Following the lag period, the interaction between the acetate and the polymer enhances the coating's permeability to the extent that the complete active dose is liberated in a short amount of time. The lag time increases as the coat thickness increases, but the drug release is independent of this thickness and is determined by the amount of salt present in the system.

b. Sigmoidal system

This comprises an ammonia-methacrylate copolymer-coated pellet containing the medication and succinic acid. Succinic acid is dissolved by the water in the medium. The permeability of the polymer film is increased by the medication inside and the acid solution. Acetic acid, glutaric acid, tartaric acid, malic acid, or citric acid are all alternatives to succinic acid. This technology was utilized to create a core that includes acid. The lag time was found to have a good in vitro/in vivo connection.

2. Stimuli induced pulsatile system

A. Temperature-induced system:

For pulsatile release, thermo-responsive hydrogel systems have been developed. 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 isopropyl acrylamide and butyryl acrylamide, Y.H. Bae *et al* created an indomethacin pulsatile release pattern in the temperature ranges of 200°C to 300°C.

B. pH-sensitive drug delivery system:

One component of this sort of pulsatile drug delivery system is immediate release, while the other is pulsed release, which releases the medication in reaction to changes 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 area can be controlled by using pH-dependent polymers Cellulose acetate phthalate, polyacrylates, sodium carboxymethylcellulose, and Eudragit E-100 are examples of pH-dependent polymers.

3. Externally regulated pulsatile drug delivery

Another approach for pulsatile medication release is to use an externally regulated system. External stimuli such as magnetism, ultrasound, electrical action, and irradiation are used to program drug release. Magnetic beads are used in the implant of a magnetically regulated system. Because of magnetic beads, drug release happens when a magnetic field is applied.

FLOATING DRUG DELIVERY SYSTEM:

One method for achieving gastric retention and appropriate drug bioavailability is to use floating drug delivery systems. For medications with an absorption window in the stomach or upper small intestine, this delivery mechanism is ideal. This has a lower bulk density than gastric fluids, thus it remains buoyant in the stomach for a long time without changing the gastric emptying rate, and the medicine is released slowly and at the specified rate from the system. The residual system in the stomach is cleared once the medicine is released. As a result, the gastric retention time (GRT) was enhanced, and the volatility in plasma drug concentration was better controlled.

The following are the most important requirements for a floating drug delivery system.

- It should gently discharge contents to act as a reservoir.
- It must produce a cohesive gel barrier.
- It must keep its specific gravity below that of the gastric contents.

VII. CLASSIFICATION OF FLOATING DRUG DELIVERY SYSTEM:

- 1) Non-Effervescent system
- 2) Effervescent system
 - a. The gas generating system
 - b. Volatile liquid containing system
- 3) Non effervescent system
 - a. Single-layer floating system

- b. Bilayer floating system
- c. Alginate beds
- d. Hollow microspheres

EFFERVESCENT SYSTEM:

Effervescent systems use gas-generating agents, carbonates (such as sodium bicarbonate), and other organic acids (such as citric acid and tartaric acid) in the formulation to produce carbon dioxide (CO₂) gas, lowering the system's density and allowing it to float upon the gastric fluid. The integration of a matrix holding a percentage of liquid, which produces gas that evaporates at body temperature, is an alternative.

1. Gas generating system:

Low-density FDDS is based on the release of CO₂ following oral delivery when it comes into contact with stomach contents. The materials are designed so that after entering the stomach, CO₂ is liberated as a result of an interaction with acidic gastric content, and then entrapped in the gel-based hydrocolloid (fig.2). It causes the dose form to float in the environment and retains its buoyancy. As a result, the specific gravity of the dose form decreases, resulting in a float on the chime. The CO₂ generating components are blended in a single layer or multi-layered form within the tablet matrix to establish a gas-generating mechanism in the hydrocolloid layer, while the medication in the other layer produces a prolonged release effect.

A. Single-layer floating tablet:

The CO₂ generating components and the medication are mixed thoroughly within the matrix tablet to create molecules. These have a lower bulk density than gastric fluids, thus they float around in the stomach for a long time, slowing down the gastric emptying rate. The drug is released from the floating system at a controlled rate, and the residual system is evacuated from the stomach when the drug has been released completely. This increases in the gut and improves control over medication concentration fluctuations in the plasma.

B. Bilayer floating tablets:

These are compressed tablets with two layers, one for immediate release and the other for sustained release.

C. Multiple Unit Type Floating Pills:

They are sustained release pills used as seeds in these systems, which are encircled by two layers. Effervescent agents make up the inner layer, while a swellable membrane layer takes up the outer layer. When submerged in dissolving liquid at body temperature, the system dips immediately and then produces inflated pills that float due to their decreased density. CO₂ generation and trapping inside the system result in a lower density.

D. Floating system with ion exchange resin:

a) Volatile liquid containing systems:

A drug delivery system's GRT can be maintained by integrating an inflatable chamber containing a liquid (such as ether or cyclopentane) that gasifies at body temperature, causing the chamber to inflate in the stomach. The device may additionally include a bio-erodible plug made of PVA, Polyethylene, or other materials that progressively dissolve, causing the inflatable chamber to release gas and collapse after a predetermined time, allowing the inflatable systems to eject themselves from the stomach spontaneously.

Intragastric floating gastrointestinal drug delivery system

Because of the floating chamber, which may be a vacuum filled with air or a harmless gas, this device can be designed to float in the stomach, while the drug reservoir is contained inside a tiny porous compartment.

Inflatable gastrointestinal delivery system

In these systems, an inflatable chamber is incorporated, which contains liquid ether that gasifies at body temperature to beget the chamber inflatable in the stomach. These systems are fabricated by loading the chamber with the pharmaceutical reservoir, which may be a medicament saturated polymeric matrix encapsulated during a gelatin capsule. After oral administration, the capsule dissolves to release the pharmaceutical reservoir alongside the inflatable chamber. The inflatable chamber automatically inflates and retains the pharmaceutical reservoir into the gastric fluid.

b) Gas generating systems

In these systems, effervescent reactions occur between carbonates/ bicarbonates salts and citric/ tartaric acid to liberate CO₂, which gets entangled in the gelatinizing matrix of the systems. Therefore, lowering its relative viscosity and making it float over the gastric fluid

NON-EFFERVESCENT SYSTEM:

1) Single Layer Floating Tablets

The floating oral delivery method is predicted to float on the gastric contents for an extended period, increasing the bioavailability of all medications that are well absorbed from the GI tract. They're manufactured by combining medication with a gel-forming hydrocolloid that swells when it comes into touch with stomach contents while maintaining a bulk density of less than one. These dosage forms are buoyant due to the air trapped within the inflated polymer.

2) Bilayer Floating Tablets

A bilayer tablet has two layers: an instant release layer that discharges the initial dose from the system, and a conventional sustained release layer. For example, a bilayer floating capsule of misoprostol, a synthetic version of prostaglandin E1 used to prevent gastrointestinal ulcers induced by the use of NSAIDs. Floating systems, swellable and expandable systems, high-density systems, bioadhesive systems, altered shape systems, gel-forming solution or suspension systems, and sachet systems are some of the methods used to prepare gastro retentive drug delivery systems. The floating dose form has been the most widely employed of these. Gas-generating systems, non-effervescent systems, and raft-forming systems are some of the floating systems. The floating oral delivery method is predicted to float on the gastric contents for an extended period, increasing the bioavailability of all medications that are well absorbed from the GI tract.

3) ALGINATE BEADS:

Freeze-dried calcium alginate would be used to create multi-unit floating dosage forms. Spherical beads with a diameter of about 2.5 mm can be made by dropping a sodium alginate solution into an aqueous calcium chloride solution, causing calcium alginate to precipitate, resulting in the production of a porous system that can maintain a floating force for over 12 hours. When compared to solid beads, which had a low residence period of 1 hour, these floating beads had a far longer residence time of over 5.5 hours.

4) HOLLOW MICROSPHERES:

A novel emulsion solvent diffusion procedure was used to manufacture hollow microspheres with pharmaceuticals in their outer polymer shell. The drug's ethanol: dichloromethane solution and enteric acrylic polymers are stirred and heated to 40°C in an aqueous PVA solution. The gas-phase created by the evaporation of dichloromethane in scattered polymer droplets developed within the interior cavity of the polymer with drug microspheres. The tiny balloons floated continuously over the surface of acidic dissolving media containing surfactant for more than 12 hours. The amount of medication released was higher at pH 7.2 than at pH 6.8. Hollow microspheres (micro balloons) with ibuprofen in their exterior polymer shells were created using a novel emulsion-solvent diffusion process.

Advantages:

- Floating dosage systems are essential technological medication delivery systems that have gastric retentive nature and provide several benefits.
- Even at the alkaline pH of the intestine, floating dosage forms such as tablets or capsules
- will stay in the fluid for a long time.
- FDDS dosage forms are beneficial in cases of diarrhea and diarrhea because they retain the medicine in a floating state in the stomach, allowing for a better reaction.
- Because acidic substances, such as aspirin, irritate the stomach wall when they come into touch with it, HBS/FDDS formulations could be advantageous for the administration of aspirin and other related medications.
- The FDDS is beneficial for medications that are absorbed through the stomach, such as ferrous salts and antacids.
- Controlled delivery of drugs.
- Reduce mucosal irritation by taking the drug slowly.
- Treatment of gastrointestinal disorders such as gastroesophageal reflux.

DISADVANTAGES:

- Many factors influence gastric retention, including stomach motility, pH, and the presence of food. Because these variables are never consistent, buoyancy cannot be anticipated.
- Drugs that irritate or cause damage to the stomach mucosa should not be designed as floating drug delivery systems.
- Due to its all-or-none-emptying method, there is a lot of variation in gastric emptying time.
- Patients should not be given floating forms right before bedtime.
- Drugs with a problem of solubility (or) stability in stomach juices are not suitable for a floating system.
- The dose form should be taken with at least a full glass of water (200-250 ml).

DISEASES AND CHRONOTHERAPEUTICS

1. Anti-asthma treatment:

It is estimated that asthma symptoms occur 50 to 100 times more at night than during the day. Many circadian-dependent factors appear to contribute to the onset of nocturnal asthmatic symptoms. For example, the levels of cortisol (an anti-inflammatory) were very high during waking hours and very low at night, and the concentration of histamine (mediator of bronchoconstriction) reached a level corresponding to the highest level of bronchoconstriction at 4:00 am. The findings also revealed that theophylline absorption slows down at night. Improved understanding of the chronobiological impact on the pathology of asthma, as well as the pharmacology and pharmacokinetics of drugs used in its management, has led to new approaches to disease management and improved patient care.

2. Wound treatment:

It is confirmed that patients with peptic ulcers often experience more severe pain at bedtime, as the rate of acid release in the stomach is much higher at night [1]. The timing of wound treatment has a significant impact on their treatment effect.

3. High blood pressure:

With high blood pressure the heart rate and blood pressure rise very early in the morning (early or early morning). Blood pressure rises from noon and is minimal at midnight. In many patients with high blood pressure, there is a marked increase in blood pressure when a person wakes up called morning or —a.m. systolic blood pressure rises pressure on waking called morning or —a.m. systolic blood pressure rises to about 3mm hg/hour in the first 4-6 hours after waking up, while the rate of diastolic blood pressure rises is about 2mm hg/hour.

4. Myocardial Infarction:

The occurrence of myocardial infarction has been shown to occur more frequently in the morning. When 34% of events occur between 6 a.m. At noon. Severe cardiac arrest and transient myocardial ischemia indicate an increase in morning frequency. Causes of this finding have been suggested by the release of catecholamine, an increase in Cortisol in platelet integration, and vascular tone. The ACE inhibitor shows significant effects when taken at night. Atenolol, Nifedipine, and Amlodipine are most effective when taken at night.

5. Rheumatoid arthritis:

Patients with osteoarthritis tend to have less pain in the morning and more at night, while those with arthritis, experience pain that often arises in the morning and lasts all day. Proinflammatory cytokines show abnormal rhythms, especially serum TNF and serum IL6, and along with other appropriate immunological parameters indicate early onset in patients with rheumatoid arthritis.

Such patients, therefore, experience joint pain, morning stiffness, and active paralysis in the early morning. Chronotherapy for all forms of arthritis using NSAIDs should be timed to ensure that the high blood pressure of the drug is accompanied by severe pain.

Arthritis:

Patients with osteoarthritis tend to have less pain in the morning and more at night, while those with arthritis, experience pain that usually rises in the morning and subsides throughout the day. Proinflammatory cytokines show abnormal rhythms, especially serum TNF and serum IL6, and along with other relevant immunological parameters show a very early onset in rheumatoid patients. Such patients, therefore, experience joint pain, morning stiffness, and active paralysis in the early morning. Chronotherapy for all forms of arthritis using NSAIDs should be timed to ensure that the high blood pressure of the drug is accompanied by severe pain.

6. Duodenal Wound:

Gastric acid secretion is very high at night. Nocturnal acid pressure is an important factor in the treatment of duodenal ulcers, and daily a bedtime dose regimen is recommended for H2 antagonists.

7. Cancer:

Chemotherapy may be more effective and less toxic when using anticancer agents to remember plant cell cycles. This way there will be less toxicity to normal tissues. The blood flow to the tumors and the growth rate of the tumor are three times greater during the daily activity phase of the circadian cycle than during the daily rest phase. The concept of Chronotherapy offers the promise of advancing current cancer treatment options. Chronotherapy, however, is not uncommon, being limited to only 50 cancer centers worldwide. Diabetes: Circadian behaviour on glucose and insulin secretion from sugar was revealed and studied. Increased blood sugar levels are found after eating.

8. Hypercholesterolemia:

Hepatic cholesterol synthesis is also found following the circadian rhythm. But the rhythm varies from person to person. There is a significant difference in the concentration of plasma mevalonate between individuals. However, cholesterol levels are usually higher at night than during the day. Diurnal synthesis is only 30-40% of daily cholesterol synthesis. High production occurs very early i.e., 12 hours after the last meal. The evening dose of HMG CoA reductase inhibitors is more effective than the morning dose.

9. Neurological Disorder:

An examination of epilepsy and seizures reveals the rhythm of chronology. It is said that the brain area with the highest concentration of noradrenergic nerve terminals and noradrenalin has a circulating rhythm of noradrenalin content.

10. Heart disease:

Cardiovascular diseases include high blood pressure and angina, or chest pain, also following a specific circulatory rhythm. Platelet concentrations increase and fibrinolytic activity decrease in the morning, leading to a related hyper state of blood coagulability. For this reason, the frequencies of myocardial infarct and sudden cardiac death increase during the amount from morning to noon. Ambulatory blood pressure measurements show significant circadian variability to detect blood pressure. This variability is affected by a variety of external factors such as race, gender, autonomic nervous system tone, vasoactive hormones, and hematological and kidney flexibility. Increased heart rate, blood pressure, unbalanced independence tone, the circulation rate of catecholamine that regulates cardiac arrhythmias show significant circadian variability and trigger gene circadian patterns for cardiac arrhythmias. Atrial arrhythmias appear to show a circadian pattern usually with high frequency during the day and low frequency at night with abnormal foci under the same long-term regulation of self-regulation as normal pacemaker tissue.

VIII. ACKNOWLEDGMENT

The preferred spelling of the word "acknowledgment" in America is without an "e" after the "g". Avoid the stilted expression, "One of us (R. B. G.) thanks . . ." Instead, try "R. B. G. thanks". Put applicable sponsor acknowledgments here; DO NOT place them on the first page of your paper or as a footnote.

REFERENCES

- [1] R. Matholiya., A. S. Dedakia. "An Approach For Controlled Drug Delivery. As Pulsatile Drug Delivery System." International Bulletin of Drug Research, 2(3): 1-21.
- [2] Mayuresh R. Rader. "A COMPREHENSIVE REVIEW ON FLOATING PULSATILE DRUG DELIVERY SYSTEM." WORLD JOURNAL OF PHARMACEUTICAL RESEARCH. 2019. 8(8), 304-329.
- [3] Vidhi R. Patel. "Pulsatile drug delivery system- A Review." ISPSR. 2015 6(9), 76-86.
- [4] Dubal Ashwini. "CHRONOTHERAPY SCIENCE AND TECHNOLOGY OF DRUGS SCHEDULING ON BASIS OF BIOLOGICAL RHYTHM." JCHRDD. 1(1), 9-18.
- [5] J. Ravi Kumar Reddy. "Review on Pulsatile Drug Delivery System." JSPR. 2009. 1(4), 109-115.
- [6] Anupama Sarawade. "FLOATING DRUG DELIVERY SYSTEM: R OVERVIEW." IJRDP. 2014. 3(5), 106-115.
- [7] R. Matholiya., A. S. Dedakia. "An Approach for Controlled Drug Delivery. As Pulsatile Drug Delivery System." International Bulletin Of Drug Research, 2(3): 1-21.
- [8] B.Kakade, D.B.Shelar, S.S.Tikole, G.S.Bamane, A.T.Ubale; "Floating Pulsatile Drug Delivery System." International Research Journal for Invention in Pharmaceutical Sciences, 2014; 2321-7855.
- [9] Davis S.S., Illum L., "Drug delivery system for challenging molecules". Int. J.pharm., 1998; 176: 1-8.
- [10] Survase S and Kumar N. "Pulsatile drug delivery: Current scenario"; CRIPS, 2007; 8(2): 2.
- [11] Anal AK. "The time-controlled pulsatile delivery system for bioactive compounds. Recent Patents on Drug delivery and formulation", 2007; 1: 73- 79.

- [12] Lavanya M, Jayanth P, Datta D, Niranjana Babu M, "Gastroretentive Drug Delivery System"; Indo American Journal of Pharmaceutical Research, 2013; 3(9): 7307-7315.
- [13] P. Patel., T. R. Desai., C. R. Matholiya., A. S. Dedakia. "Pulsatile Drug Delivery System: A Review" 1-32.
- [14] S. Patel., M.K.Modasiya., V.M.Patel., A.K.Patel. "Design and Development Of Floating Pulsatile Drug Delivery System Using Meloxicam". International Journal of Pharmaceutical Research And Bio-Science, 2012; 1(2): 215-235.
- [15] G. Pragna., B. Shravani., N. G. Raghavendra Rao., "Pulsatile Drug Delivery System: An Overview" International Journal Of Pharmaceutical Development And Technology, 2013; 3: 97-105.
- [16] V. Prasanth., M.P. Modi., S. T. Mathew. "Pulsatile: A Tool For Circadian Rhythm – A Review". Journal Of Drug Delivery & Therapeutics, 2012; 2(1): 58-65.
- [17] S. Survase, N. Kumar. "Pulsatile Drug Delivery: Current Scenario". Current Research & Infor. Pharm. Sci., 2007, 8 (2): 27-33.
- [18] L. X. Liu, X. C. Wang. "Solubility-modulated monolithic osmotic pump tablet for atenolol delivery". Eur. J. Pharm. Biopharm., 2008, 68: 298-302.
- [19] U. Conte, L. Maggi. "A flexible technology for the linear, pulsatile and delayed release of drugs allowing for easy accommodation of difficult in vitro targets". J. Control. Release, 2000, 64: 263-68.
- [20] S. Lee, S. W. Kim, S. H. Kim. Et al. "Drug release from hydrogel devices with rate-controlling barriers". J. Membr. Sci. 1980, 7: 293-303.
- [21] Gajbhiye ND, Vilasrao JK, Kisan RJ, Anand UK et al, "Pulsatile Drug Delivery System", Journal of Pharmacy Research 2010; 2:120-123.
- [22] Rasve G, Borade G, Deshmukh S, Tagalpallewar A, "Pulsatile Drug Delivery System: Current Scenario", International Journal of Pharma and Bio Sciences 2011; 2:332-343.
- [23] Janugade BU, Patil SS, Patil SV and Lade PD: "Pulsatile drug delivery system for chronopharmacological disorders: an overview". Journal of pharmacy research 2009; 2(1):132- 143.
- [24] Bussemer T, Otto I, Bodmeier R, "Pulsatile drug delivery systems Crit Rev, The Drug Carrier Syst" 18(5),2001, 433-458.
- [25] Rompicharla.B, Suria P, "A comprehensive review of Pulsatile drug delivery system", International Journal of Pharmacy Research, 3(3), 2012, 106-108.



IJRTI