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A REVIEW ON NOVEL DRUG DELIVERY TECHNOLOGY CONSISTING OF FLOATING DOSAGE FORM WITH PULSATILE DRUG RELEASE

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ABSTRACT

The formulation of pulsatile release drug delivery systems is a reservoir or matrix system, which can include one or more units and is intended to deliver drug levels that are either constant or virtually constant over a prolonged period of time. One such system is pulsatile drug delivery, which holds great promise and benefits patients with chronic conditions like arthritis, asthma, hypertension, etc. by delivering medication at the appropriate time, place, and amount. This increases patient compliance and provides both spatial and temporal delivery. The fundamental argument for the usage of pulsatile release of the medications is where a steady drug release is not desirable. It provides an overview of these systems' release profiles, formulation characteristics, and most recent technological advancements. These systems are useful for medications with chronopharmacological characteristics, such as anti-arrhythmic and anti- asthmatic ones, that need to be taken at night. A single dosage form included a first dose of the medication, one release free interval, a second dose of the medication, subsequent release free intervals, and drug release pulses. One of the main objectives of medication delivery is to be able to administer a therapeutic agent and bioactive chemical to a patient in a pulsatile release profile.

KEYWORDS: Chronotherapy, Floating pulsatile release tablet, burst release, Rupturable, Controlled release drug delivery, Rupturable, Erodible, lag time, swelling index.

INTRODUCTION

Most bodily functions fluctuate throughout the day. The sleep-activity cycle is a key element

of the human circadian rhythm, influenced by our genetic predispositions, and it impacts bodily performance during both daytime and nighttime (over a 24-hour cycle).[1] Each bodily system experiences optimal functioning at certain times that align with these rhythmic patterns. This study primarily aimed to conceptualize a floating pulsatile drug delivery system that ensures no drug release during floating and in the proximal small intestine, followed by a controlled release in the distal small intestine. To enhance patient adherence, it is crucial to implement chronotherapeutic drug release for treatments targeting rheumatoid arthritis, osteoarthritis, spondylitis, cardiovascular diseases, and various hypertensive conditions. The floating pulse drug delivery system facilitates medication release at designated locations and ensures the drug exerts its effects at specific times.[2]

CHRONOBIOLOGY

Chronobiology is the field of science that examines the biological mechanisms of diseases in relation to temporal patterns. The term "chrono" refers to time, while "biology" denotes the study of living organisms.[7]

CHRONOTHERAPY

Chronotherapy refers to the synchronization of biological rhythms with medical treatment.

CHRONOTHERAPEUTICS

Chronotherapeutics is the field focused on administering medications in alignment with the natural rhythms of a disease over a defined timeframe. Recent findings suggest that the timing of medication intake by patients may be more crucial than previously acknowledged.

BIOLOGICAL RHYTHMS

1. **Ultradian Rhythms:** Ultradian Rhythms are biological cycles that take place more than once within a 24-hour period. An example of this is the 90-minute sleep cycle.
2. **Infradian Rhythms:** Oscillations exceeding 24 hours are referred to as Infradian Rhythms, which occur at a frequency of less than one cycle within a 24-hour period. An example of this is the monthly menstrual cycle.
3. **Circadian rhythms:** Circadian rhythms are internal, self-regulating cycles that occur naturally.[8]

MECHANISMS OF BIOLOGICAL TIME KEEP

A hereditary master clock network, consisting of the paired suprachiasmatic nuclei (SCN)

located in the pineal gland and hypothalamus, governs circadian rhythms. This central clock system is characterized by the cyclic nocturnal secretion of melatonin from the pineal gland, along with the rhythmic expression of specific clock genes, including perl, per2, per3, bmal, clock, and CRY, among others, along with their respective gene products.[9]

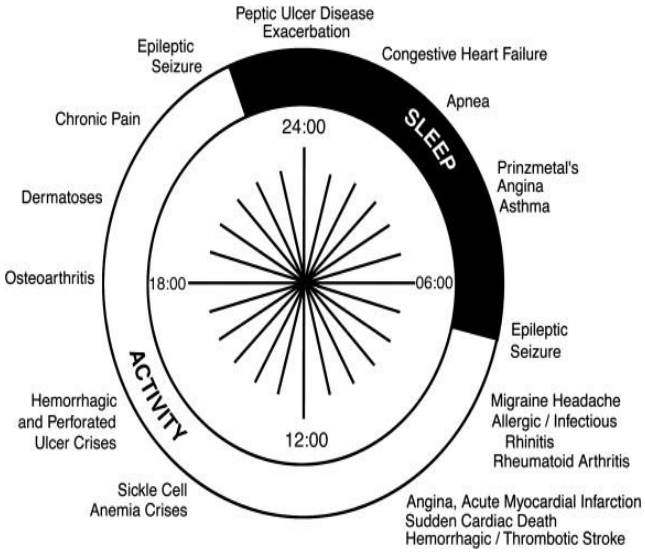

Fig: 1 Circadian rhythm showing diseases.

CIRCADIAN RHYTHM SHOWING DISEASES

Table-1: The interplay between circadian cycles and the emergence of health conditions.

Disease or Syndrome	Circadian Rhythmicity
Allergic Rhinitis	Worse in the morning/upon rising.
Asthma	Exacerbation more common during the sleep period.
Osteoarthritis	Symptoms tend to intensify during the afternoon and evening hours.
Angina Pectoris	ECG changes more common in Early morning.
Myocardial Infarction	Incidence greatest in early morning.
Stroke	Incidence higher in the morning.
Sudden Cardiac Death	This trend suggests that the frequency of incidents trends to increase shortly after individuals rise from sleep.
Peptic Ulcer Disease	Worse in late evening and early morning hours.

CARDIOVASCULAR DISEASES

1. **Coronary Artery Disease (CAD):** The accumulation of plaque in the coronary arteries can result in angina, characterized by chest pain, or may lead to heart attacks.
2. **Hypertension:** High blood pressure can damage the heart and blood vessels, increasing the risk of heart attacks, strokes, and kidney problems.
3. **Heart Failure:** A medical condition characterized by the heart's inability to pump blood efficiently, resulting in symptoms like breathlessness and tiredness.

4. **Arrhythmias:** Irregular heartbeats that may impair the heart's capacity to effectively circulate blood.
5. **Stroke:** A stroke happens when the brain's blood flow is disrupted, which can be caused by a blockage (ischemic stroke) or by bleeding (hemorrhagic stroke).
6. **Peripheral Artery Disease (PAD):** This condition is characterized by the constriction of peripheral arteries, primarily in the legs, resulting in diminished blood circulation and symptoms such as leg pain during physical activity.
7. **Aortic Aneurysm:** A bulge in the wall of the aorta, the main artery that carries blood from the heart to the entire body, poses a significant health risk. Should this protrusion rupture, it could result in serious and possibly life-threatening hemorrhaging.
8. **Valvular Heart Disease:** Heart valve disorders can affect one or more of the valves, resulting in complications related to blood circulation within the heart. Notable examples of these conditions are aortic stenosis and mitral valve regurgitation.
9. **Congenital Heart Defects:** Congenital heart defects refer to structural irregularities of the heart that exist from birth. The degree of these defects can vary significantly, from minor issues to intricate conditions that might necessitate surgical treatment.
10. **Endocarditis:** Endocarditis is an infection that affects the inner lining of the heart, specifically the chambers and valves. This condition usually arises when bacteria enter the bloodstream and attach themselves to the heart tissue.
11. **Myocarditis:** Inflammation of the cardiac muscle, frequently resulting from viral infections, can hinder the heart's capacity to pump blood efficiently.
12. **Pericarditis:** The inflammation associated with pericarditis affects the pericardium, which serves as a crucial barrier for the heart. Understanding this condition is essential for diagnosing and managing potential health issues related to cardiac function. This condition can lead to acute chest pain and may arise from infections or various other medical issues.
13. **Cardiomyopathy:** Cardiomyopathy encompasses a range of conditions that impact the heart muscle, resulting in difficulties with the heart's capacity to effectively circulate blood. The various types encompass dilated cardiomyopathy, hypertrophic cardiomyopathy, and restrictive cardiomyopathy.
14. **Pulmonary Embolism:** A blockage in a pulmonary artery within the lungs, typically resulting from blood clots that have migrated from the legs (known as deep vein thrombosis), can pose a serious risk to life if not addressed swiftly.

GENERAL SYMPTOMS

- **Chest Pain or Discomfort:** A common characterization of this sensation is a feeling of pressure, tightness, or discomfort in the chest area. This feeling can radiate to various areas, including the arms, back, neck, jaw, or abdomen.
- **Shortness of Breath:** It can happen during exercise or while at rest and may be associated with wheezing or a sensation of breathlessness.
- **Fatigue:** Uncommon fatigue or weakness that persists despite rest and can disrupt daily activities.
- **Palpitations:** Irregular or rapid heartbeats that may be experienced as a fluttering or pounding sensation in the chest.

SPECIFIC CONDITIONS

1. **Coronary Artery Disease (CAD)**
   - **Angina:** Engaging in physical activities or experiencing stress frequently leads to chest pain or discomfort.
   - **Heart Attack:** Intense chest pain, feelings of nausea, excessive sweating, difficulty breathing, and unease in various regions of the upper body.

2. **Hypertension (High Blood Pressure)**

Typically presenting without symptoms, it can lead to headaches, dizziness, and nosebleeds in more severe instances.

3. **Heart Failure**
   - **Swelling (Edema):** Especially in the legs, ankles, or abdominal area.
   - **Persistent Cough:** Frequently characterized by mucus that is white or has a pink hue.
   - **Sudden Weight Gain:** Fluid retention has occurred.

4. **Arrhythmias**
   - **Irregular Heartbeat:** Experience of irregular heartbeats or a rapid heartbeat.
   - **Dizziness or Light-headedness:** Could result in episodes of fainting or near-fainting.

5. **Stroke**
   - **Sudden Numbness or Weakness:** Notably on one side of the body.
   - **Confusion or Trouble Speaking:** Challenges in comprehending spoken language or

experiencing slurred articulation.

- **Abrupt changes in vision:** Affecting either a single eye or both eyes simultaneously.
- **Sudden Severe Headache:** The cause remains unidentified.

6. Peripheral Artery Disease (PAD)

- **Leg Pain:** Discomfort in the legs, characterized by cramping sensations in the legs or buttocks. While walking typically subsides with periods of rest.
- **Coldness:** The lower leg or foot in relation to the opposite leg.

CLASSIFICATION OF FLOATING DRUG DELIVERY

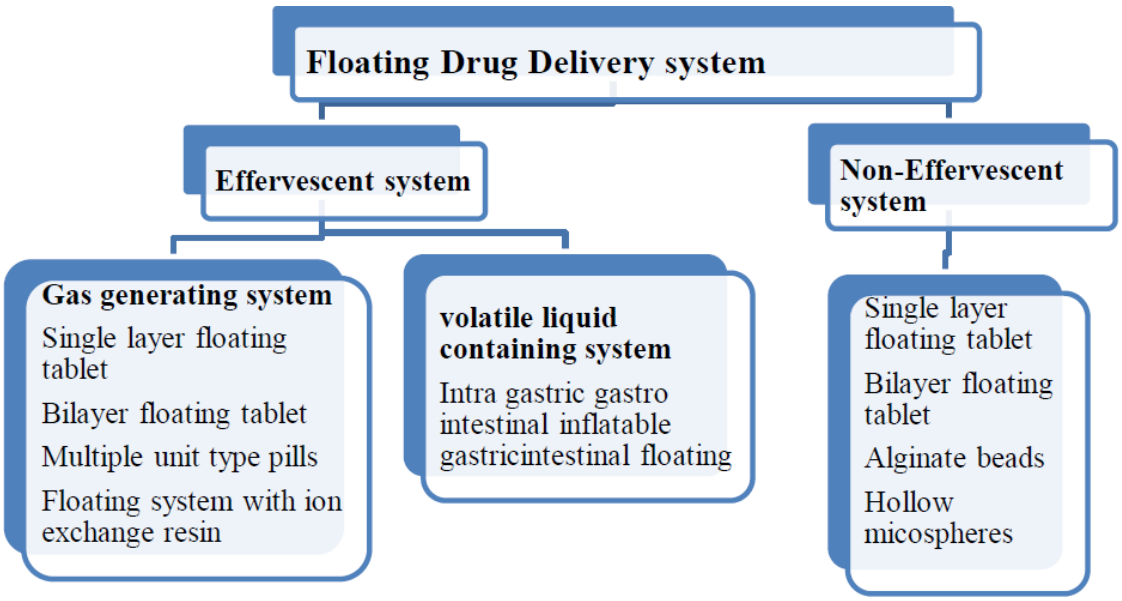

Fig. 2: Floating pulsatile drug delivery system.

Floating drug delivery systems can be categorized based on two formulation variables

- ❖ Effervescent
- ❖ Non-effervescent.

1) Effervescent Floating Dosage Forms

These systems are matrix types formulated using various effervescent agents such as sodium bicarbonate, tartaric acid, and citric acid, along with swellable polymers like methylcellulose and chitosan. They are engineered to release carbon dioxide upon interaction with the acidic environment of the stomach, while simultaneously trapping gas within the expanding hydrocolloids, which imparts buoyancy to the dosage forms.

2) Non-effervescent Floating Dosage Forms

Non-effervescent floating dosage forms are formulated using matrix-forming polymers such as polycarbonate, polyacrylate, polymethacrylate, and polystyrene, which are combined with gel-forming or swellable cellulose-based hydrocolloids. The formulation process entails thoroughly blending the active pharmaceutical ingredient with the hydrocolloid, which subsequently creates the gel structure. Upon oral administration, this dosage form swells when it comes into contact with gastric fluids, achieving a bulk density of less than 1. The buoyancy of the dosage form is attributed to the air trapped within the expanded matrix. The resulting gel-like structure acts as a reservoir, facilitating the sustained release of the drug.

ADVANTAGES

1. Medications can be degraded in the upper gastrointestinal tract environment, such as peptide and protein molecules.
2. It allows for a reduction in drug dosage while maintaining therapeutic efficacy.
3. The reduction in side effects is significant.
4. It reduces the potential for drug interactions by decreasing the activity of cytochrome P450 isoenzymes.
5. The influence of food on the efficacy of medications is diminished.
6. Patient adherence to treatment is enhanced.
7. It enables the effective management of a range of medical conditions.
8. Programmed delayed release enables multiple doses to be administered in a single formulation.
9. It permits targeted release for localized treatment of specific conditions.
10. Drug release remains unaffected by variations in pH levels within the gastrointestinal tract.
11. Additionally, the viscosity of the contents in the lumen and the rate of agitation in the GI tract are taken into account.
12. The release of the drug is not influenced by changes in pH levels throughout the gastrointestinal tract.
13. It supports extended activity during the day or night.
14. It circumvents first-pass metabolism for substances like proteins and peptides.
15. It addresses biological tolerance, as seen with transdermal nitroglycerin.
16. It allows for specific targeting within the intestine, such as the colon.
17. It is utilized for time-controlled administration of hormones and medcations.

18. It aids in mitigating gastric irritation that may be induced by specific medications.
19. It improves the stability of pharmaceuticals within gastric fluids.
20. It reduces the overall daily cost for patients by requiring fewer dosage units in treatment.
21. It protects the mucosal lining from irritating medications.
22. It prevents drug loss due to extensive first-pass metabolism.
23. Metabolism is particularly relevant for proteins and peptides.
24. It avoids the development of biological tolerance, as seen with transdermal nitroglycerin.[17-18]

DISADVANTAGES

1. The floating system is inappropriate for medications that encounter challenges related to solubility or stability within the gastrointestinal environment.
2. These systems necessitate a substantial amount of fluid in the stomach for effective drug delivery.
3. Only drugs that are significantly absorbed throughout the gastrointestinal tract and experience considerable first-pass metabolism can utilize this system.
4. A major challenge is the inconsistency in manufacturing reproducibility and efficacy.
5. It involves a large number of process variables.
6. The manufacturing process is batch-based.
7. Production costs are higher.
8. The manufacturing of dosage forms necessitates the expertise of qualified professionals.
9. A 24-hour sleep-wake syndrome may develop if an individual sleeps for more than 24 hours during treatment. While this occurrence is relatively rare, the associated risk level remains undetermined.
10. Individuals may occasionally experience a lack of sleep.
11. Productivity may decline during chronotherapy, and remaining awake until the next scheduled sleep may be more manageable.
12. Individuals will need to allocate time away from their regular busy routines to accommodate this time-intensive therapy.
13. Medical oversight is essential for this therapy, and regular consultations with sleep specialists are advised.
14. Individuals must remain awake until the next sleep schedule, necessitating engagement in activities to help them stay alert.
15. Those undergoing therapy may experience fluctuations in body temperature, feeling

either unusually hot or cold at times.[19-20]

CLASSIFICATION OF PULSATILE DRUG DELIVERY SYSTEMS

VARIOUS APPROACHES OF PULSATILE DRUG DELIVERY

The pulsatile drug delivery system is primarily divided into three key categories;

- **Time controlled pulsatile drug delivery**
- **Stimuli induced pulsatile drug delivery**
- **Externally regulated pulsatile drug delivery**

1. Time controlled pulsatile drug delivery

A. Single unit pulsatile systems

1. Capsule based systems E.g. Pulisincap system
2. Capsular system based on Osmosis

a) 'PORT' System

b) System based on expandable orifice

c) Delivery by series of stops

d) Pulsatile delivery by solubility modulation

3. Pulsatile system utilizing barrier coatings that can erode or dissolve.

a. The chronotropic system

b. 'TIME CLOCK' System

c. Compressed tablets

d. Multilayered Tablets

4. Pulsatile system with rupturable coating

B. Multiparticulate / Multiple unit systems:

1. Pulsatic system with rupturable coating

E.g. Time –controlled Explosion system (TCES)

2. Osmotic based rupturable coating system

E.g. Permeability controlled system

3. The administration of pulsatile doses was enhanced through alterations in membrane permeability

E.g. Sigmoidal release system.

TIME CONTROLLED SYSTEM

1. SINGLE UNIT PULSATILE SYSTEM

i. Capsule based system

A capsular system consists of an insoluble capsule body containing a plug and a medication. The plug is gradually eliminated through mechanisms like erosion, dissolution, or swelling. During a designated lag time, the medication is released in pulses from the capsule body, with the duration of this lag time being extended by the plug, which is displaced by swelling or erosion. The medication is encapsulated in a capsule that is not soluble in water, which constitutes the system. A swellable hydrogel stopper is used to seal the medication inside the capsule body. When the capsule encounters the dissolution fluid, the plug begins to expand. When the predetermined lag time is completed, the plug is freed from the capsule, leading to an expedited delivery of the medication. The duration of this lag time is affected by the dimensions of the plug and its placement within the capsule. The capsules open end is closed off with an expandable hydrogel plug, which responds to the surrounding dissolving medium or gastrointestinal fluids, leading to its expulsion from the capsule after the established lag period. This is followed by the swift release of the medication. The lag time can be modified by altering the dimensions and positioning of the plug. To ensure rapid release of water-insoluble medications, effervescent agents or disintegrants may be incorporated, while enteric coating can mitigate gastrointestinal irritation associated with this formulation.[17]

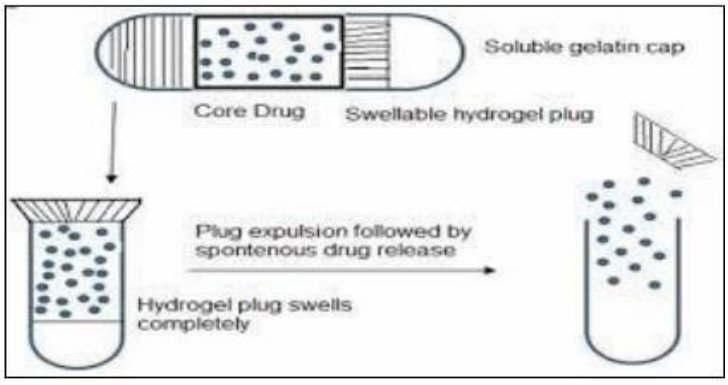

Fig. 3: Capsule based system.

ii. Delivery systems with rupturable coating layer

These systems consist of an external layer that controls the release of a porous, water-insoluble coating capable of mechanical rupture. Recently, various devices featuring an outer rupturable layer and an inner swellable layer have been developed, primarily utilizing hard gelatin capsules and tablet cores. The films rupture may occur due to the addition of osmotic,

effervescent, or swelling agents within the reservoir. This mechanism allows for the timed release of the drug.

To formulate their tablet system, Sungthongjeen employed spray-dried lactose and microcrystalline cellulose for the drug core. The core was then treated with the swelling polymer croscarmellose sodium, followed by the application of an outer rupturable layer made of ethyl cellulose. Ongoing innovations in osmotic drug delivery are being achieved through the implementation of swellable core technology, which includes a formulation with one or more delivery ports, a core tablet containing the drug, and a water-swellable component.[18]

iii. Osmotic systems

The structure consists of capsules encased in a semi-permeable membrane. Inside each capsule lies an undisclosed medication that integrates pharmaceutical formulations with osmotically active components. When the semi-permeable membrane encounters a dissolution fluid, it allows water to enter, resulting in increased pressure. After a certain delay, this pressure facilitates the expulsion of the insoluble plug.[19]

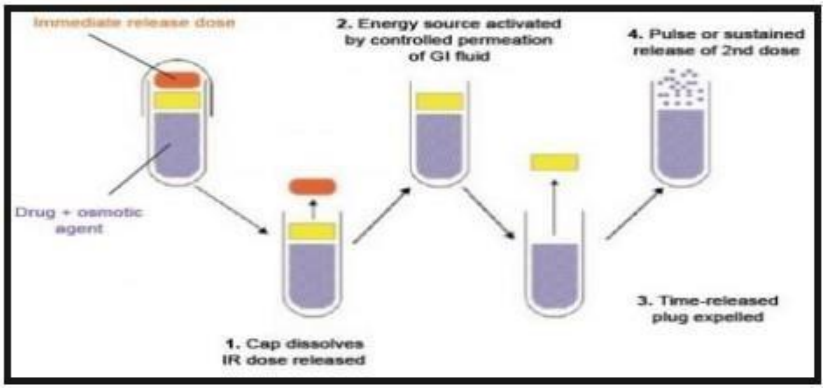

Fig.4: Osmotic pulsatile drug delivery system.

iv. Delivery systems equipped with degradable coating layers

In these systems, the degradation or corrosion of the outer layer, which encases the medication's core, regulates the drug's release. By increasing the thickness of the outer layer, the active ingredient can be released in a controlled, time-dependent fashion. Building on this concept, an oral dosage form was created that allows for a gradual release of the medication following ingestion. This system features a core that houses the drug, surrounded by a hydrophilic swellable polymeric coating made from HPMC. The hydrophilic coating

gradually interacts with aqueous fluids, thereby postponing the drug's release.

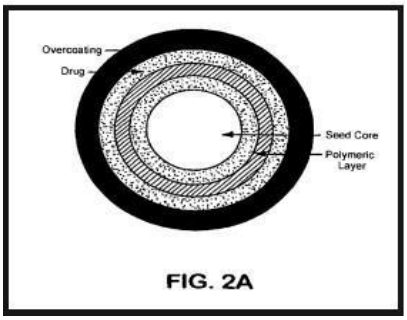

Fig.5: Delivery systems with erodible coating layers.

2. MULTIPLE UNIT PULSATILE DRUG DELIVERY SYSTEM

I. Systems based upon change in membrane permeability

The drug in this system is made to release the medication in doses spread out over the course of a day's use, creating a pulsatile, curving decision over time. Where in the medication is prepared in a capsule with three different kinds of pellets inside. A medication plus a water-soluble modifying ingredient (such as sodium chloride) make up the core of each pellet. The high of binding agents such as pvp holds the core in place. Every core has a hydrophilic agent and a water-insoluble, water-porous layer developing around it. The type of pellet utilized to make the medication formulation determines the coating's thickness. When the pellets enter the stomach, they are influenced by its environment, leading to the dissolution of the capsule upon contact with the physiological conditions. The amount of osmotic agent in the pellet, the percentage of hydrophobic agent in the coating, and the virtual thickness of the pellets all influence the rate of release. In order to prevent it from interfering with the prearranged release time intervals, ph is coated on dependent materials.

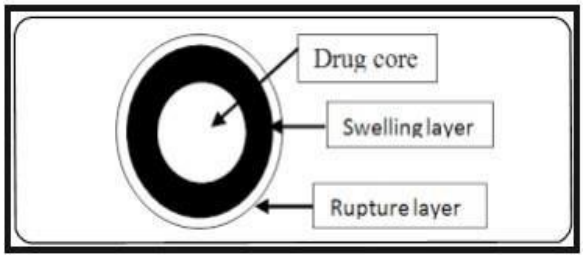

Fig.6: Delivery Systems with Rupturable Coating Layer.

II. Pulsatile systems with rupturable coating

The rupture of the membrane is regulated by a pulsatile drug delivery mechanism. The timing of the release is influenced by both the thickness of the coating and the amount of water-

soluble polymer employed in the formulation of the pulsed release system. Although the surface coating's thickness can vary, each particle's internal core composition remains the same. Compared to a single unit pulsatile system, a Multiparticulate system has greater benefits. These features include a short duration of stomach retention, the ability to combine units with different release profiles, and the elimination of the risk of dose dumping. Numerous polymers and their corresponding devices are employed to facilitate a pulsatile drug release mechanism. Devices that increase the stomach residency of dosage forms and have a lag phase followed by burst release are categorized based on the type of polymer utilized. [21] Such innovative drug delivery methods have been tried for.

I. Chronopharmacotherapy focuses on the timing of medication administration for diseases that exhibit circadian rhythms in their pathophysiology.
II. This approach is particularly relevant for medications that have an absorption window in the upper gastrointestinal tract.
III. Optimizing drug delivery in accordance with biological rhythms can enhance therapeutic efficacy and minimize side effects.
IV. For drugs having ph dependent solubility e.g. Verapamil HCL.
V. **Gastro retentive systems**: To enhance the absorption of drugs that are poorly soluble in lower gastrointestinal tract by allowing them to remain in the upper part of the gastrointestinal tract for an extended period, thereby preventing degradation.

PRESS COATING TECHNOLOGY

Press coating also referred to as double compression coating, compression coating, or dry coating, is an old technique first proposed by Noyes in an 1896 patent.

The press coating technique offers many advantages, such as protection of hygroscopic, light sensitive, oxygen labile, and acid-labile drugs, isolation of incompatible drugs from each other, and provides a method for both sustained drug release and modification of the drug release profile. A press-coated tablet generally consists of a central core tablet encased in an external coating layer. A press- coated tablet generally consists of a central core tablet encased in an external coating layer. This outer layer envelops the inner core, making the choice of materials for the coating crucial, as it greatly influences the tablet's overall performance. Factors such as the mechanical strength of the coating, the characteristics of drug release, and the stability of the tablet are all significantly affected by the selected materials for the outer layer. Combination dosage forms can also be developed, allowing two

active ingredients to address distinct regions of the gastrointestinal tract.

The press-coated tablet may consist of a fast disintegration or modified release core, coated by compression with a solid barrier, commonly made of polymeric material, a diluent (as a release modifier) and drug (for both rapid or extended release). The formulation of press coated tablets can be adjusted to achieve various drug release profiles by altering the distribution of the active ingredient and the types of polymers utilized in both the core and outer coating. These modifications can lead to tailored drug release mechanisms that respond to specific conditions such as time, pH levels, or microbial presence, allowing for targeted delivery within particular areas of the gastrointestinal tract. Thus, press-coating may be classified as a chrono pharmaceutical technology, in that it provides a solid dosage form for drug delivery in a pulsatile fashion rather than continuously, and Oral administration is conducted at specified times and locations.[24]

THE TECHNIQUES EMPLOYED IN THE MANUFACTURING PROCESS OF PRESS COATING

Numerous studies in the literature detail the application of the press-coating technique for optimizing drug delivery from tablets, and these findings are presented as comprehensively as possible. The manufacturing process of press-coated tablets involves multiple stages. Initially, the inner core tablet is formulated and subsequently compressed under specific conditions. The die of the tableting machine is pre-loaded with shell-coating materials to create a powder bed, into which the compressed inner core tablet is positioned at the center. Additional materials for the external coating layer are then applied, following which the outer coating layer is tightly compressed around the inner core tablet. Additionally, schematic representations demonstrating the preparation of different varieties of press-coated tablets are included. The possibility of schematic designs for preparing various types of press-coated tablets is shown in Fig. below.

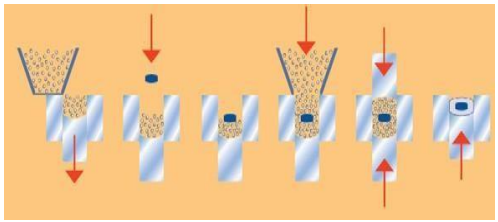

Fig 7: The steps taken in the creation of press coating.

- Prefilling the half amounts of outer coating materials into the die.
- Putting the inner core tablet on the powder bed of outer coating materials.
- Centring.
- Filling the residual half amounts of outer coating materials.
- Compression
- Ejection of press-coated tablet from the die.

CONCLUSION

The main focus of chronotherapeutic formulation of cardiovascular diseases is to optimally deliver the drug in higher amounts in the early morning hours and lower amounts at night. Because systolic blood pressure and diastolic blood pressure rapidly rise in the early morning atleast 15 to 25 mm Hg and reach highest levels late in the day. It is common for SBP and DBP to decrease by 10% to 20% while an individual is asleep, reflecting a notable difference from their daytime measurements.

Pulsatile drug delivery systems or chronotherapeutic drug delivery systems are designed to release drug as a pulse manner after a pre-determined lag time to increase the drug release at the site of action of a disease according to circadian rhythm at right time and right amount, press coating or compression coating are used. This techniques increase the lag time and shows release according to the need of pathophysiology of disease compared to conventional tablet there by increasing bioavailability.

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