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ORIGINAL ARTICLE

Pulsatile Drug Delivery System Utilizing Innovative Technology

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ABSTRACT

Drugs might be released immediately or over time. Pulsatile medication release systems, on the other hand, have been increasing in popularity in recent years. Many medications or therapies could benefit from pulsatile drug release, in which the drug is released rapidly after a predetermined lag time. Pulsatile release systems come in pairs: multi and separate pulse. Rupturable dose forms are a prominent type of single-pulse device. Other methods have a drug-containing centre covered by both a swelling surface and a semi - permeable barrier polymer layer or membrane that is semipermeable but not soluble. The full action of the swelling film, and the permeability and mechanical qualities of the polymer covering, have a large impact in the lag time before the rupture. Many significant features in living organisms are controlled either by pulse or temporary release of active ingredients at a particular spot and duration. As a result, innovative drug delivery systems must be created to accomplish pulsed dispersion of a specified quantity of drugs in simulating the action of organisms while reducing adverse reactions. Special emphasis has been paid to the thermolabile poly (N-isopropylacrylamide) and its derivatives hydrogels. Designing drug delivery devices, hydrogels, and other materials. Micelles allows for thermal stimuli-regulated pulsed drug release. So, pulsatile medication delivery is one of those systems that has a lot of promise for people with long-term conditions like arthritis, asthma, and high blood pressure because it gives drugs at the right time, in the right place, and in the right amount.

Keywords: Pulsatile release of drug, chronotherapy, circadian, and time lag

INTRODUCTION

The oral route of drug administration is often regarded as the most popular and user-friendly method of medication administration, with the highest level of patient compliance. Medication administration systems are traditionally concerned with maintaining a steady or prolonged medication production with the objective of reducing drug concentration fluctuations in the system to increase treatment effectiveness and avoid negative impacts.

Circadian clocks are self-sustaining, 24-hour recurring internal oscillation. [1] Internal biological clocks connected to the sleep-wake cycle generally coordinate circadian rhythms. Human metabolism, physiology, behavior, sleep pattern, and hormone synthesis are all regulated by the circadian rhythm. [2] Many diseases, like heart disease and asthma, follow the body's circadian rhythm. Scheduling and changing medicine administration to match the disease's circadian rhythm can be helpful.

The field of chronotherapy is related to the distribution of pharmaceuticals across time in accordance with the intrinsic activities of a disease, whereas chronotherapeutic is associated with the synchronization of circadian clock and medical treatment. In the treatment of a range of illnesses, chronotherapeutic advantages have been proven. [3] Circadian rhythms have been shown to have an impact on disease processes and physiological events. Myocardial infarctions, for example, are more common in the mornings. These results indicate that medication delivery and treatments be modified to get an efficient drug quantity in the quickest time possible. This will be performed using the pulsatile drug delivery technique of an appropriate pharmaceutical. [4]

Certain disorders, such as asthma and stomach ulcers, might benefit from oral pulsatile administration. Pulsatile drug delivery refers to the ability of a controlled drug release formulation that distributes medicine at various speeds throughout time, ranging from very lowest to highest. It should also be willing to release its medicament at a certain moment or in a specific part of the digestive organs. The term "tablet pulsatile release systems" refers to a variety of technologies. The majority of tablet formulations are reservoirs with a barrier covering. Formulations such as Pulsi cap have been developed in addition to capsule-based pulsatile release methods. [5]

Pulsatile Drug Delivery System Advantages [6,7]

1 an extended period of daytime and nighttime activity.
2 Dose size, adverse effects, and dosage frequency are all reduced.
3 Patient compliance has improved.
4 The patient pays a lower daily cost since fewer dose units are necessary.
5 A drug affects heart rhythms in response to a body function or disease.
6 Drugs that target a specific site, such as the colon,
7 mucosa protection from irritant medicines.
8 Extensive first-pass metabolism prevents drug loss.
9 Stay away from biological tolerance (e.g., Transdermal nitroglycerine).

Limitations of the Pulsatile Drug Delivery System [8]

1 In the case of a multi-particulate drug delivery system, there are multiple manufacturing procedures.
2 The drug burden is minimal.
3 The release is incomplete.
4 Variability in vivo in a single-unit pulsatile drug delivery system.
5 In the case of youngsters and the elderly, drug dose modification is not an option.
6 There is no way to stop taking the medicine right away.

Diseases that necessitate the use of a pulsatile drug delivery method: Pulsatile diseases are those that necessitate the use of a pulsatile device as a drug delivering system.

The pharmacokinetics and/or pharmacodynamics of medications are not constant during the first 24 hours in diseases when the body's rhythmic circadian organization is significant. Hyperlipidemia, asthmatic attack, duodenal ulcer, arthritis, diabetic mellitus, cancer disease, neurological disorders, cardiovascular diseases and colonic delivery are among the diseases that exhibit such a temporal pattern. As an example,

Hyperlipidemia is a condition in which a person's cholesterol levels are elevated. During hepatic cholesterol synthesis, a circadian pattern is seen [9]. As a result, lipid production is greater at night than during the day, peaking in the early morning. Studies with HMG-CoA reductase inhibitors have revealed that nighttime administration is more effective than morning dosing. [10] During the Asthmatics have their sleep disrupted on a regular basis. Because of the role of circadian rhythms in the development and management of asthmatic, asthmatic patients' bronchial sensitivity appears to increase in the evening. Healthy lung capacity fluctuates throughout the day, with a lower point in the early hours of the morning. Because bronchoconstriction and symptom aggravation vary depending on the time of day, asthma is well-suited to chronotherapy. Asthma chronic therapies include orally corticosteroids, aminophylline, and B2-agonist. [11]

Studies on animals and people have shown that chemotherapy may be more effective and less risky if anticancer medications are given at certain periods and take advantage of the cycles of carcinoma cells while causing less harm to good cells [12]. When compared to the daily rest period, blood flow to tumor

cells was three to four times higher during the circadian activity phase. [13]

Numerous studies have been conducted on the circadian oscillations of insulin and glucose in diabetics. Through consistent baseline production and food-stimulated secretion, insulin therapy seeks to replicate the normal rhythm of insulin release in normal individuals. [14]

A method for releasing drugs from a pulsatile drug delivery device: A various release of drug mechanisms from PDDS have been proposed: [15]

1 Diffusion is the initial phase of the procedure. When a particle comes into contact with liquid in the digestive system, water diffuses into the inside of the particle, the drug solutions flow through the releasing layer to the outside.

2 Erosion: Some coatings are made to deteriorate over time, liberating the drug they contain.

3 Osmosis**:** When water is allowed to enter the particle under the correct conditions, an osmotic pressure can be generated within the particle's interior. Through the coating, the medication is driven out of the particle and into the environment.

Pulsatile delivery system classification.

1 Pulsatile release system with a timer is classified into two types Single-unit (e.g., tablet or capsule) and multiple-unit systems

A Single Unit Systems:

1 Capsular system: Capsules are used to create the bulk of single-unit systems. The medicine is released from the insoluble capsules as a "pulse" into the body after a rest period is controlled by a barrier that is turned away by enlargement or erosion. Pulsicap technique, which encloses the drug reservoir in a water-insoluble capsule, is one example. The medication contents were sealed inside the capsule body using a swellable hydrogel stopper. The plug pushed itself outside the capsule after a lag time whenever this capsule comes in contact with a dissolving solution, instantly releasing the drug as seen in figure (1). The hydrogel plug was produced utilizing hydroxypropyl methyl cellulose HPMC, poly ethylene oxide, poly methyl methacrylate and poly vinyl acetate pva in various viscosity categories. The plug's lengths and point of entrance into the capsule were responsible for determining the lag phase. [16,17]

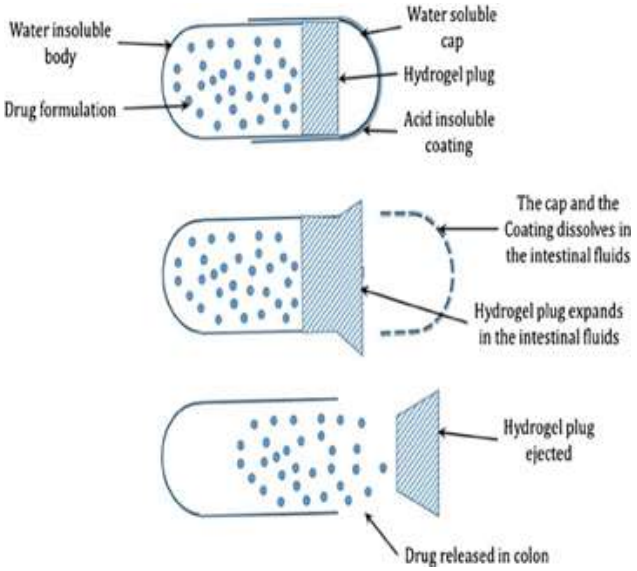

Figure 1: Schematic Diagram of Capsular System

2 Osmosis based system: A medication and a water-absorptive osmotic agent are placed in chambers in this configuration and are separated by a movable barrier. Pulsatile delivery is accomplished by pausing repeatedly all along the interior layer of the capsule. A series of pauses along the capsule's inner wall are used to deliver pulsatile delivery. These blocks inhibit the

partition from moving, but as the osmotic pressure rises over a certain point, they are overcome one by one. This method was used to give porcine somatotropin. Water is selectively transported into the capsule reservoir via the walls of osmotic delivery capsules (also known as "osmotic pumps"). Osmotic pressure across the capsule wall is caused by a liquid -chemical in the capsule interiors, allowing the capsule to absorb water through these walls. However, in most situations, it is a different agent specifically selected for its capacity to draw water and segregated from the advantageous chemical at one end of the capsules. The water-attracting agent may be the beneficial agent whose controlled release is required. (18,19)

3 Port® System: A gelatin capsule with a semi-permeable membrane covering makes up the Port® System (For instance, cellulose derivatives). In addition to the medication formulation, the capsule also included an osmotically active chemical and an insoluble plug. Figure illustrates how when this capsule interacts with the dissolving fluid, water diffuses across the semi - permeable barrier, increasing overpressure that eventually causes the plug to expel as shown in figure (2). The time lag depends on the coating's thickness.[20]

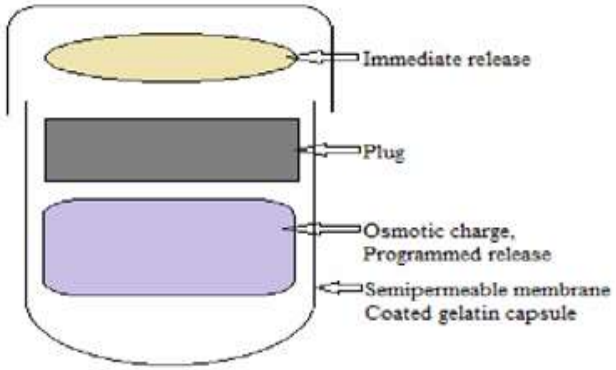

Figure 2: Port System

4 Membrane delivery system that is soluble or erodible: In such devices, the disintegration or eroding of the applied outermost surface that surrounds the core containing the medicine regulates the production of the medication. The thickness of the outer layer may be altered to guarantee the active component releases in a time-dependent manner. As an example, consider the chronotropic system in the image below, which has an external enteric coating as an option and a drug-containing center wrapped in HPMC.

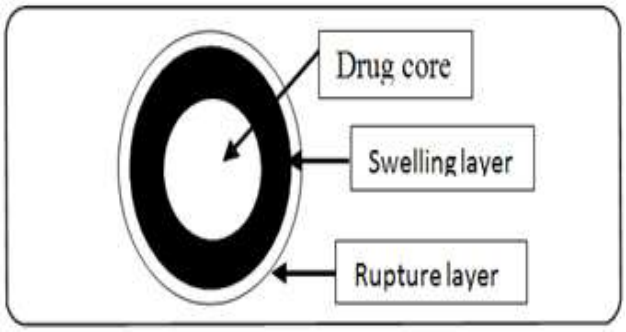

Figure 3: Delivery System with Soluble or Erodible Membranes

B Multi unite System: These are reservoir-type devices that are frequently housed in a Capsule body and have rupturable or changeable permeability coatings. [23]

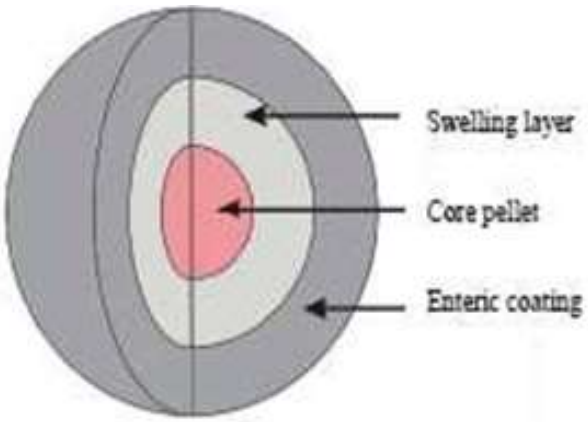

Figure 4: Hypothetical design of multi particular pulsatile system

1 Systems Based on Change in Membrane Permeability: These systems are made up of a large number of pellets split into two or more populations. Every particle is made of a water-permeable, water-insoluble polymeric membrane that surrounds a drug-containing core as well as an osmosis agent. By incorporating a hydrophobic, water-insoluble material into it. The film coating of each population of pellets in the dosage form varies as from coatings of another group of particles in the pharmaceutical formulations in terms of the speed at which fluid moves through from the center as well as the speed at which medicine spreads out from the core. The particle expands when the osmosis agent dissolves, controlling the pace at which the medicine spreads into the environment around the user. A succession of pulsatile administers of the therapy are produced by a single dosage form since each populations of particles release the drug into the environment successively. [24]

2 **Pulsatile System with Rupturable Layers/ Membranes:** The puncturing effect produced by covering the single components with effervescent or swollen substances, much like the single-unit method. Pulsatile drug delivery system that is made up of a number of particles that are split into a number of different delivery units, each with its own makeup. The membrane rupture was employed to control medication distribution (Fig. 6). The amount of water-soluble polymer used to create the pulsed release and the thicknesses of the coating were both used to control the release time. The internal content of each particle was the same, but the thicknesses of the outside coating layer changed. [25]

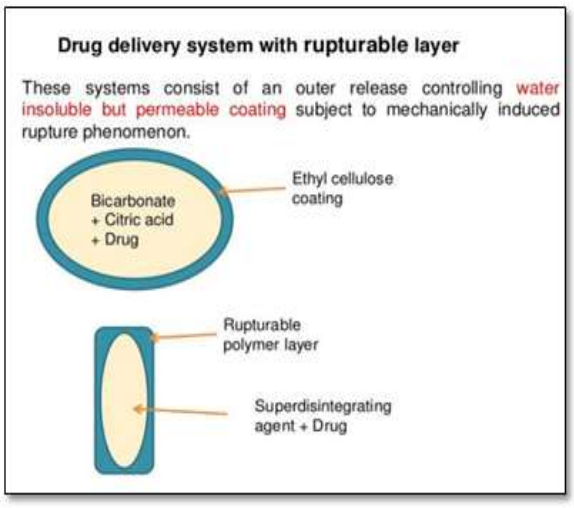

Figure 5: Drug Delivery System with Rupturable Layer

1 Classification of pulsatile drug delivery based on internal stimuli

A A system that is temperature-induced: For pulsatile medicine delivery, body temperature is an essential internal cue. The polymer in thermally hydrogel systems expands or contracts through temperature, regulating the release of drugs when the polymer is swelled. Drugs are released from hydrogels by diffusion below 32°C, but above this temperature, owing to the formation of a hydrogel layer on the skin surface, the release is completely stopped (on-off release control). [26]

B Chemical Stimuli Responsive PDDS: Chemical stimuli for pulsatile drug release are one of the most well-studied stimuli. The release of medicines from the PDDS may be aided by changes in human biological makeup. Smart gels, glucose-responsive insulin secretory systems, inflammatory mediators, pulsatile release systems, and glucose-responsive insulin secretory systems are all instances of glucose-responsive insulin secretory systems. [27]

1 Glucose-responsive insulin release devices: In such a system, a pH-sensitive hydrogel containing glucose oxidase immobilized in the hydrogel is used. Glucose oxidase turns glucose to gluconic acid as blood glucose levels rise, causing the pH of the system to alter. As a consequence of the pH shift, the polymer expands, causing insulin to be released. pH-sensitive polymers include N, N dimethylaminoethyl methacrylate, chitosan, and polyol.

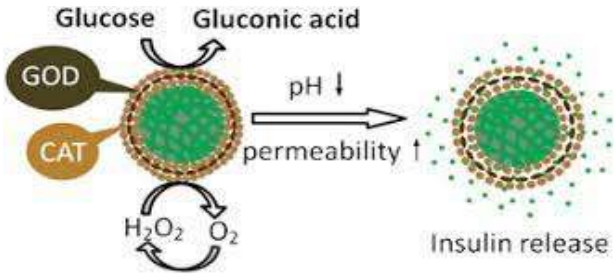

Figure 6: Glucose-responsive insulin release induced by enzyme

2 Pulsatile release device triggered by inflammation: When injuries and fractures are exposed to physical or chemical stress, they generate inflammation at the wound sites. During inflammation, these inflammation-responsive cells produce hydroxyl radicals. They utilized hyaluronic acid (HA), which is broken down by free radicals or the enzyme hyaluronidase. However, when HA is injected into inflamed regions, hydroxyl radical destruction is generally prominent and rapid. Anti-inflammatory medications, including HA gels as novel implanted drug delivery systems, may therefore be utilized to treat inflammatory illnesses like rheumatoid arthritis. [28]

3 pH-sensitive drug delivery system: The fact that the pH levels in various regions of the digestive tract vary has been used by a pH-dependent device. Using pH-dependent polymers, drug release at a specific location may be produced. Polyacrylates, cellulose-acetate and carboxymethylcellulose are examples of pH-sensitive polymers. These polymers are used in the small intestine as enteric coating materials to deliver active compounds. For example, Eudragit in colon-targeting systems. [29]

3 Advance technology of pulsatile drug delivery: Externally controlled systems employ external stimuli to train drug release, such as magnetic, ultrasonic, electrical effects, and irradiation. [30]

A Magnetically Induced Pulsatile Release: By incorporating magnetic materials such as magnetite, iron, nickel, cobalt, and others into tablets or capsules and using the external effect of a magnetic field to change the time, rate, and extent of drug absorption into the stomach or gastric intestines, we can position the drug at a specific location or slow down its access to unfavorable areas. [31,32]

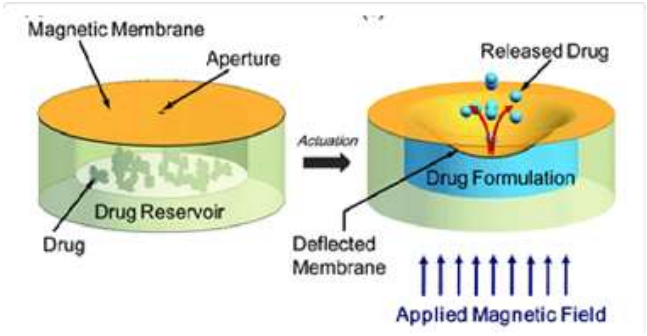

Figure 7: Magnetically Induced Pulsatile Release

B Electro Responsive Pulsatile Release: Medication release is aided by the influence of an applied electric field on a rate-controlling membrane containing polyelectrolyte, which is found in electrically responsive delivery systems. The electric field is generally what causes flexure and shrinkage in electro responsive hydrogels. This delivery method uses a poly (acrylamide-grafted-xanthan gum) hydrogel for novel transdermal administration of ketoprofen. [33]

4 Marketed Technologies of Pulsatile Drug Delivery

A Pulsincap TM technology: A non-disintegrating half-capsule body with a hydrogel plug at the open end and a water-soluble cap on top makes up this device. The whole unit is covered with an enteric polymer to prevent the issue of variable stomach emptying. When this capsule comes into touch with the dissolving fluid, it swells, and the plug, after a short pause, pushes itself outside the capsule, releasing the medication quickly. [34]

B DIFFUCAPS ® Technology: Diffucaps technology allows for the development and commercialization of novel, controlled-release delivery techniques for once- or twice-daily administration of single medicines or drug combinations with pH-dependent solubility profiles or poor solubility in physiological fluids. A novel process developed specifically for weak, basic medications involves the incorporation of a pharmaceutically acceptable organic acid or a crystallization-inhibiting polymer onto inert cores, followed by the coating of the drug-layered beads with unique functional polymers. [35]

C Three-dimensional printing: Rapid prototyping (RP) is a technique that uses three-dimensional printing (3DP). It's a ground-breaking solid free-form manufacturing technique that's been used to create complex pharmaceutical medicine devices. Powder processing and liquid binding components are used in prototyping to build accurate layers. 3DP may also aid with the controlled release of many medications in a single dosage form, as well as the administration of poorly water-soluble medicines, peptides, and proteins, as well as very toxic and potent pharmaceuticals. [36]

D Codas (Chronotherapeutic - Oral Drug Absorption System) technology: It is a multi-particle device with a 4–5-hour delay in pharmacological release that was created for nighttime medication delivery. The amount of non-enteric release-controlling polymer given to drug-loaded beads is what causes this delay. The water-soluble polymer progressively breaks down when digestive fluid comes into contact with the polymer-coated bead, allowing the medication to permeate through the coating's pores. Drug release may be regulated thanks to the water-insoluble polymer's continued barrier function. pH, posture, or diet have no impact on the rate of release.[37]

E Geomatrix TM: Recently, a novel continuous medication release mechanism in the form of a multi-layer tablet built on Geomatrix Technologies was unveiled. It comprises one or both impermeable or semi-permeable polymers coating materials applied to one or both of the bases of the hydrophilic matrix core, which contains the active ingredient. The Geomatrix TM technologies allow configurable levels of controlled drug release since it can release two different drugs at differing rates from a single tablet. To achieve controlled release, a multilayered tablet with two essential features is being used: hydrophilic polymers like hydroxypropyl methylcellulose (HPMC) and surface-controlling barrier. Barrier layers control the actively load core area that is available for medication release when exposed to fluid.[38]

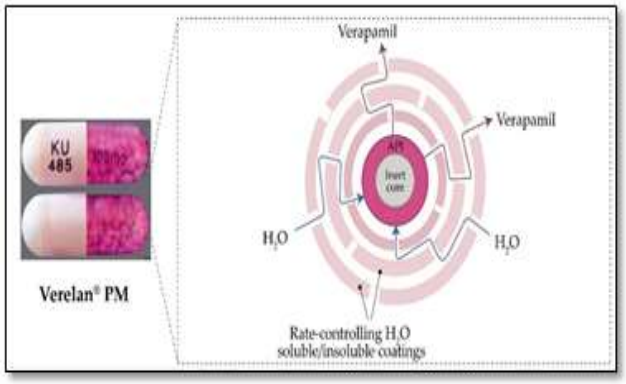

Figure 8: Codas

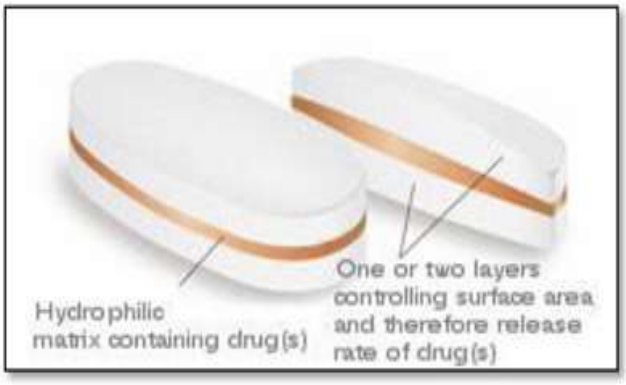

Figure 9: Geomatrix

F Diffutab: Delivery to specified regions and tailored release profiles are made possible by diffutab technology. Using a combination of wax and hydrophilic polymers, Diffutab regulates medication release via the diffusing and eroding of a matrix tablet. Diffutabs are especially useful for medicines and high-dose medications that only need to be taken once daily. It may be used for both soluble and insoluble materials. [39]

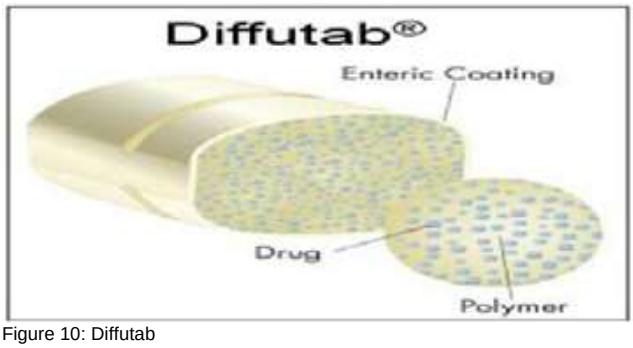

Figure 10: Diffutab

G Covera-HS: At the moment, Covera-HS is the only controlled-release verapamil formulation approved to treat both hypertension and angina pectoris. Covera-HS comes in 180 mg and 240 mg pills, and it's meant to be taken before night. Early in the morning, when blood pressure and heart rate are at their

greatest, Covera-HS is delivered at its highest concentration. Medication administration is minimal during sleep, when blood pressure and heart rate are at their physiologic lowest point. [35]

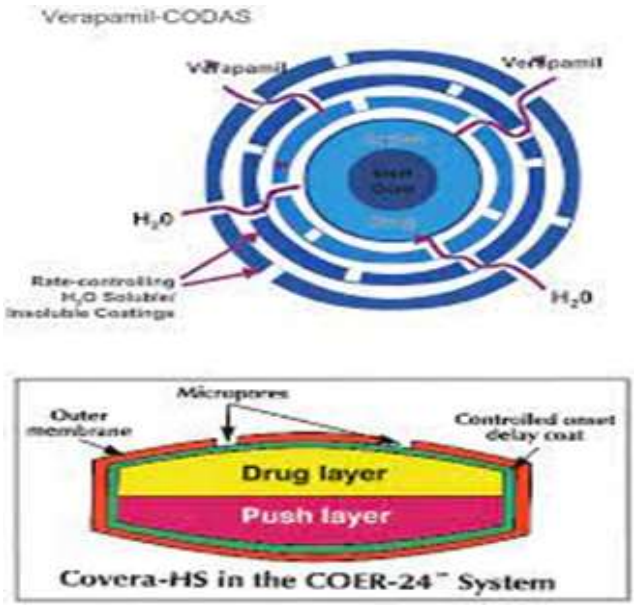

Figure 11: Covera

H Orbexa: Orbexa technology is a multi-particulate technique for granulation-based products that allows for maximal medication loading. Crystallization spheronization and extrusion processes are used in Orbexa technology to create beads with a regulated size and density. These flexible beads may be covered with active polymer membranes for better release flow control, making them suitable for usage with delicate molecules like enzymes.Stomach safety, delay release, extended release, site-specific delivery, pulsatile delivery, complex release patterns, isolation of incompatibles, and combination products are all made possible by Orbexa technology. Orbexa particles may be put in capsules or sachets for single-dose administration. [40]

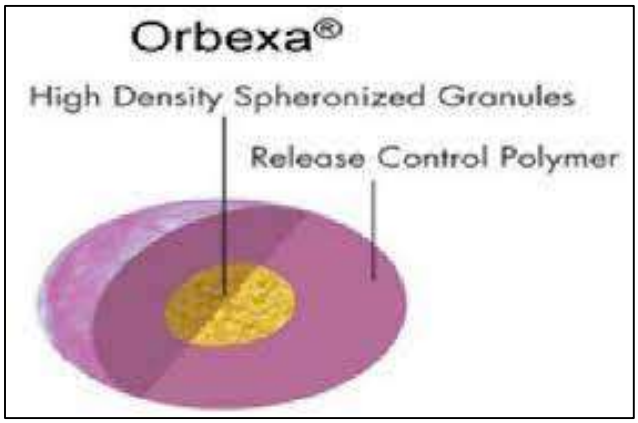

Figure 12: Orbexa

CONCLUSION

The most frequent and recommended form of administration is by mouth. In general, sustained and controlled-release drugs offer the intended effect, albeit their therapeutic efficacy is limited for illnesses or disorders that need therapy that follows the disease's biological cycles. Because medication release is managed according to the body's circadian cycle, PDDS will effectively alleviate this problem. Drugs must be given to a particular location and at a certain time to suit the disease's pathophysiological requirements. A number of technologies based on the pulsatile release concept have been created, developed, and offered by a variety of firms.

Regardless, and in contrast to commonly used dose forms. The pharmaceutical industry is currently figuring out how to commercialize PDDS in tablets and capsules on a large scale. Until the pharmaceutical industry can overcome the barriers to commercialization of PDDS, drug therapy for certain extremely common illnesses or disorders in the community would be more successful with full therapeutic benefit and minimal side effects.

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