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Pulsatile Drug Delivery System: A Review

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Abstract
Pulsed drug delivery systems (PDDS) are essentially time-controlled drug delivery devices in which the mechanism controls the lag time independently of external factors such as intestinal motility, pH, enzymes, etc. A pulsatile drug release, in which the drug is delivered rapidly after a predefined lag period, may be advantageous for a variety of drugs or therapies. Drugs are often released either immediately or gradually. Pulsatile drug release systems, however, have drawn more attention in recent years. Many medications or treatments may benefit from a pulsatile drug release, in which the drug is delivered quickly following a predetermined lag time. There are two types of pulse release systems: single-pulse and multiple-pulse. The family of single-pulse systems known as rupturable dose forms is widely used. One such method is pulsatile medication delivery, which promises to help patients with chronic conditions including arthritis, asthma, and hypertension by administering drugs at the appropriate times, locations, and dosages. Systems for pulsatile medication delivery may lead to major advancements in the treatment of several illnesses. Technologies including Pulsincap, Diffucaps, CODAS, OROS, and PULSY Saremarketed. The press coating process is a simple and unique technology that yields tablets with a programmable lag phase and a quick, or rate-controlled, drug release after ingestion, among its numerous advantages. These tablets may be made without the need of specialized coating equipment or solvent. When selecting the best chronopharmaceutical technology, consideration should be given to both production ease and cost-effectiveness.

Keywords: PDDS;Pulsatile Drug Delivery System, Chronobiology, Sustained Release, Lag Time, Circadian Rhythms, Chronotropic system, Osmosis.

1. Introduction

The largest market sector for medication delivery overall is oral drug delivery. It is the most favored method of administering drugs. The drug concentration is kept within the therapeutic window for an extended amount of time in oral controlled-release systems, which guarantees sustained therapeutic activity. Such a release pattern is not appropriate for some illnesses that require the medicine to be released after a lag period. To put it another way, they need a pulsatile medication delivery system. Since the medicine is delivered fully after a predetermined lag period, pulsatile systems are becoming increasingly popular. In order to provide both spatial and temporal delivery and improve patient compliance, pulsatile medication administration is site-specific and time-specific. The rapid and temporary release of a specific quantity of molecules within a brief period of time following a predetermined off-released period, also known as a lag time, is known as pulsatile drug delivery. Pulsatile release is the term used to describe such a release pattern.

Cargo-targeted drug delivery accounts for the majority of the drug delivery market. For a longer duration, oral controlled-release systems maintain the drug release concentration in the therapeutic range, guaranteeing long-lasting therapeutic advantages. Certain diseases require medication to be

administered after a delay, and this kind of release is ineffective. Under the biological clocks of clinical circumstances, pulsatile medication is a technique in which the drug is delivered abruptly following a predetermined, substantial delay or time interval. This is the case when medications that include proteins and peptides undergo significant metabolic degradation. Drug resistance may arise with long-term treatment, which might have detrimental effects. Since the necessary dosage concentration at a certain moment is available, the odds are reduced in this instance.

Both intrinsic mechanisms, i.e., devices designed to operate consistently in spite of important physiological parameters (temperature, pH, ionic strength), and external signals (such as chemical, thermal, electric, and magnetic stimuli) can initiate the pulsatile/delayed release process. Circadian or ultradian fluctuation patterns of illness symptoms are the only viable targets for oral delivered pulsatile delivery devices due to gastrointestinal transit restrictions. In fact, they may be helpful in treating conditions including cardiovascular disease, rheumatoid arthritis, bronchial asthma, and sleep issues that typically manifest in the early morning or at night. In these situations, pulsatile-release medications may provide a quick pharmacological reaction after the nightly dosing schedule without requiring the patient to be exposed to the drug molecule for an extended period of time or causing sleep disturbances, which would lower compliance. A example PDDS graph that deviates from a regulated release is shown in the image. [1] [2]

Systems for pulsatile drug delivery have several advantages. some of them are listed below:

- These systems can be used for extended periods of time during the day or at night.
- They reduce the size, cost, and frequency of dosages, which ultimately reduces side effects and improves patient adherence.
- The drug adapts to the circadian rhythms of diseases or physiological functions.
- A medication can be directed to a specific location, like the colon.

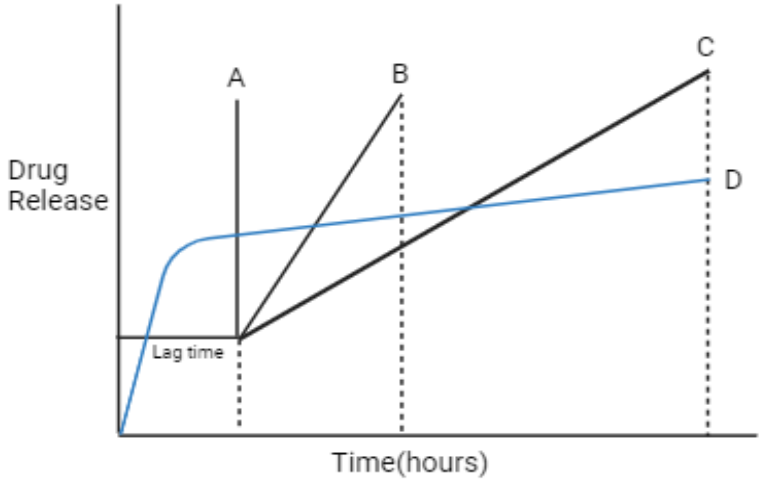

Figure 1

(A) Sigmoidal release based on mechanical properties; (B) delayed release after lag time; (C) sustained release after lag time; and (D) prolonged release without lag time are among the several drug delivery methods schematically depicted in Figure 1.

- Additionally, they shield the mucosa from irritant medications.
- They also stop drug loss due to significant first-pass metabolism.
- They avoid peak-valley variations and maintain consistent medication levels at the site of action.

The creation of "pulsatile drug delivery systems [5]" is prompted by diseases that require a periodic pulse of therapeutic concentration rather than continuous medication levels. Immediately following a specified off-release period, a certain quantity of drug molecules are released in a brief and quick manner in these devices. Figure 3. Numerous methods, such as pH-dependent systems, time-dependent systems, microflora-activated systems, etc., are available for pulsatile distribution and may be tailored to the characteristics of the drug molecule and the physiology of the illness. The pulsatile drug delivery techniques and emerging technologies that are being used on an industrial scale are the main subjects of this review. [3]

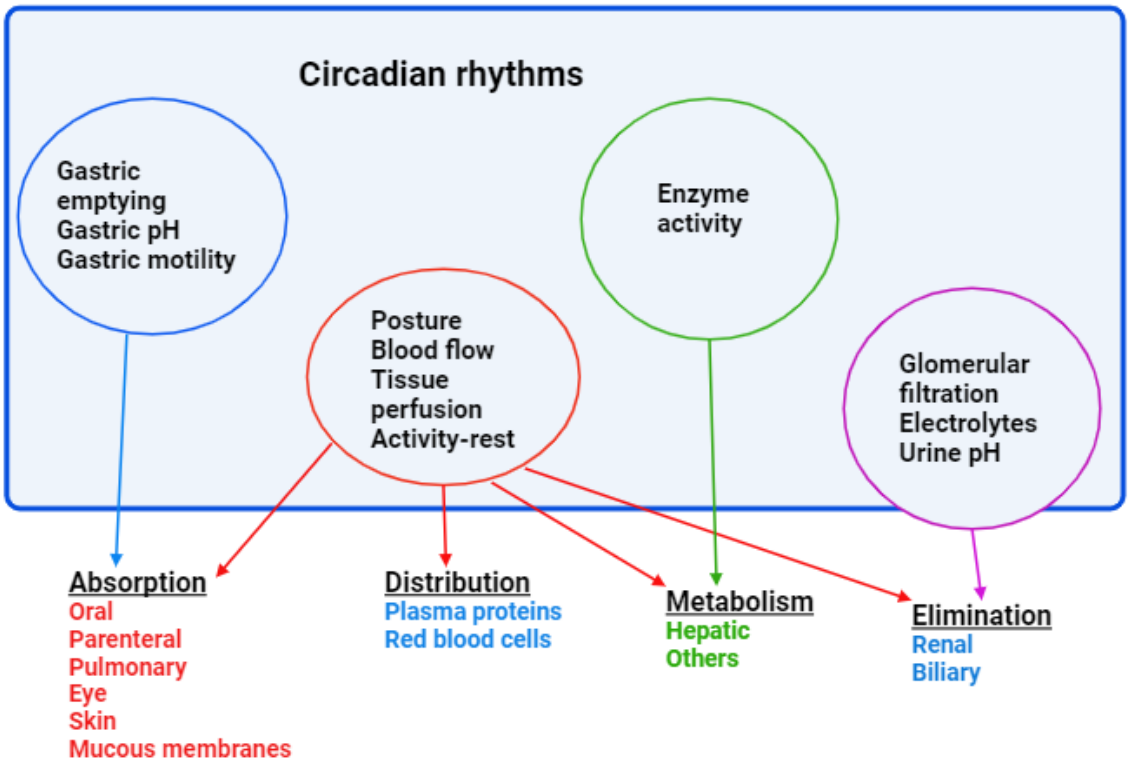

Figure 2: Circadian rhythms

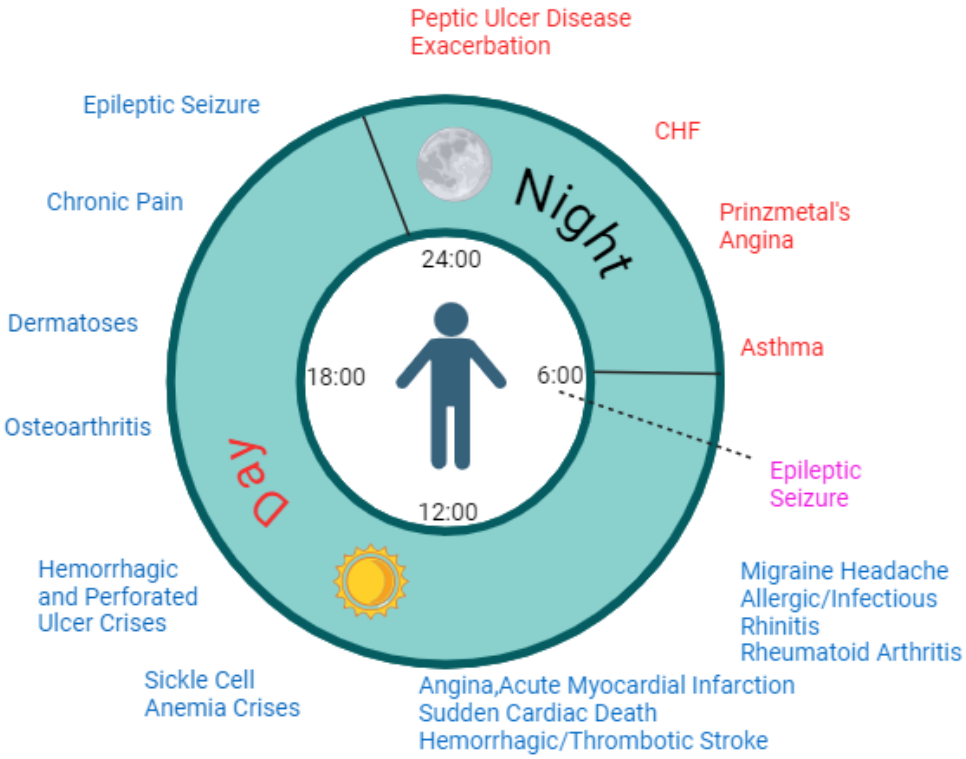

Figure 3: Time clock for diseases

1.1 Advantages

- Reduced variability between and between subjects
- Predictable, repeatable, and brief stomach residence duration
- Enhanced bioavailability. Better tolerance and fewer negative effects. Reduced chance of local irritation.
- No chance of dosage dumping
- Design flexibility; increased stability
- Better patient comfort and compliance
- Development of a distinctive release pattern
- Expansion of patent protection
- Globalization of the product and victory over competitors [3] [4].

1.2 Disadvantages

- Several formulation phases
- A large number of process variables
- A lack of manufacturing efficacy and repeatability
- Higher production costs, and the requirement for modern technologies
- Personnel have the necessary training and skills for manufacturing[3]

Table 1: Patents involving different approaches for pulsatile drug delivery technologies

Mode of drug delivery	Title (number)	Rationale for chronotherapy and features of patented systems
Oral capsular based	Methylphenidate in pharmaceutical dose form for pulsatile administration (US65550136)	disorder of attention deficit, system that combines immediate and delayed release tablets to deliver three pulses at various times
Oral capsular based	Pulsatile particles drug delivery system (US5472708)	A time-controlled device that may distribute medication into the gut using release-controlled polymers for angina and hypertension
Oral tablet based	Pharmaceutical tablets that can release active ingredients at different intervals (US4865849)	When rheumatic sickness causes morning pain, the system allows the medicine to be released in phases that are spread out so that high hematic drug levels can be achieved at various times.
Oral tablet based	Controlled release flutamide composition (US5162117)	The innovation for prostate cancer offers a controlled release form that can provide both an IR dosage and a second pulsed delayed release dose.
Capsule based (delivery device with orifice)	Delivery devices with pulsatile effect (EP0627231)	The area of invention is in the pulsatile distribution of nutrition and medications. The design and placement of the orifice, the thickness of the band composed of the elastic material, the viscosity and surface tension of the active agent formulation, and the selection of the band's elastic material all contribute to the pulsatile effect.
Transdermal device	A transdermal drug delivery device that delivers a first dose of medication (US5352456)	Depression and anxiety, as well as a drug delivery system that uses a pulse as flux to transfer medication through unbroken skin. The permeability of the backing layer to the volatile enhancer determines how long the pulse lasts.
Transdermal device	Pulsatile transdermal administration of physiologically active substances using a medical device (US4698062)	Nitroglycerin supply in steady state flux for two time periods is related to angina pectoris and chronic heart failure.
Hydrogel system	Stimulus-sensitive hydrogel-based pulsatile drug delivery device (US 5226902)	The invention pertains to the delivery of drug-loaded hydrogels that, in response to internal or external stimuli like temperature or pH changes or chemical reactions, deswell and release pharmaceuticals pulsatilely. [4]

2. Chronobiology

All living things have biological rhythms, which are essential for carrying out physiological processes in a way that prevents the environment from exhibiting noticeable, predictable variations over time. Any level of living things has biological rhythms, which may be categorized into three groups based on the length of their cycles: i) circadian rhythms, which last around 24 hours; ii) ultradian rhythms, which last less than 24 hours; and iii) infradian rhythms, which last more than 24 hours. Most of the biological mechanisms of: i) the endogenous circadian rhythmicity; ii) the neurophysiological mechanisms of the photic system that allow its external resetting; and iii) the neuroendocrine mechanisms of internal rhythm synchronization have been explained by chronobiology, which has focused on studying these biological rhythms in recent years. All of these systems are set up to execute particular tasks at predetermined periods throughout the day. Furthermore, the emergence of the areas of chronopharmacology and chronotherapeutics has been spurred by the description of certain biological rhythm diseases and rhythm issues at the cellular and even molecular level. Recent research has shown that the timing of medication regimens can improve the outcome in certain chronic conditions, and that the occurrence of serious and life-threatening medical events, such as myocardial infarction and stroke, as well as the manifestation and severity of symptoms of chronic diseases, such as allergic rhinitis, asthma, and arthritis, are influenced by the body's circadian rhythm.

When consumed, injected, infused, breathed, or administered topically at various biological times of the day and night, the same major circadian time structure can significantly alter the kinetics and dynamics of numerous kinds of drugs. Changes in the body's physiological and pathological processes need changes in the plasma concentration of drugs. Chronotherapy is a novel medical treatment method brought about by this.

2.1 Capsule-shaped delivery systems provided with release-controlling polymers.

Numerous innovations describe capsules that include several tablet, bead, granule, or particle components to provide various article highlights. Changes in the body's basic circadian rhythmic structure indicate the necessity for chronotherapy. New developments in time-controlled systems, such as pulsatile drug delivery systems that satisfy chronotherapeutics criteria with superior drug delivery capabilities, are demonstrated by recently released patents. For the time-controlled release of oral dosed active components, a vast array of alternative design methods (such as capsule and tablet) and technologies (such as multi-particulate and osmotic systems) have been developed.

One of the inventions uses a capsular dosage form, where the first tablet releases the initial intracellular release (IR) of a therapeutically effective dose of active agent. The second and third tablets then release one or two "delayed release" doses of active agent, resulting in a twice or three times daily dosing profile. Disintegrants such sodium starch glycolate and microcrystalline cellulose are included in the immediate-release tablet. Bioerodible, hydrolyzable, gradually water soluble, or enzymatically degradable polymers (such as ethyl cellulose, hydroxypropyl cellulose, cellulose acetate, and enteric polymers) and plasticizers (such as triacetin, propylene glycol, tributyl citrate, caster oil, and acetylated monoglycerides) are among the coating materials for the delayed release. In order to simulate a twice-daily dosing profile, the dosage form offers roughly 8–12 hours of lag time with one IR and one delayed release dosage unit; in order to simulate a three-times-daily dosing profile, the dosage form offers 7–9 hours of lag time between each released dose with one IR and two delayed release dosage units.

The medication, a binder like polyvinyl pyrrolidone, and a dissolution-controlling polymer like high viscosity hydroxypropylmethylcellulose make up the active core, which was made via granulation or extrusion and spheronization. The permeability of the backing layer to the volatile enhancer determines how long the pulse lasts.

The capsule has two compartments: one has the medicinal substance, and the other holds an agent that attracts water. The divider keeps the contents of the two compartments from combining. The elastic material that surrounds the aperture in the capsule's end wall is what opens and closes the orifice, constituting the device's complete wall.

2.2 Tablet-shaped delivery devices having a barrier layer that is rupturable, soluble, or erodible.

Many different types of oral pulsatile delivery methods have been developed. Drug reservoirs with an exterior release-controlling, water-insoluble, yet porous covering that is susceptible to mechanically induced rupture phenomena make up ruptureable systems. After the devices are submerged in the aqueous fluids, the membrane breaks apart partially or completely after a programmable amount of time, exposing the inner drug formulation to the bulk medium directly. The inclusion of swellable, osmotic, effervescent additives or superdisintegrants in the drug reservoir causes the inner core to expand, which

in turn causes the film to rupture due to an increase in outer pressure. Specifically, the outer rupturable layer was made of dry and wet ethylcellulose (EC), methacrylic copolymer (EudragitÒ RS), and AquacoatÒ ECD films with varying qualitative and quantitative compositions in plasticizers and pore-former; the hydrophilic swellable polymer in the composition was made of polyvinyl alcohol, cross-linked PVP, and low viscosity hydroxypropyl methylcellulose (HPMC) (MethocelÒ E5). In this study, Gazzaniga et al. examined single or multiple unit cores coated with hydrophilic, swellable HPMC polymers of varying viscosity grades. These coating systems experienced increasing permeability, swelling, erosion, and/or dissolution phenomena following hydration.

The core swells as the swelling agent absorbs water, pushing on the covering until it ruptures, releasing the medication. The pace of swelling may be decreased, and the time to explosion can be extended and managed, by decreasing the rate at which water enters the pellet's interior that contains the swelling agent. A similar type of pharmaceutical tablet dosage form was described, which included a film coat to cover the taste of the core when taken orally, a tablet core with the antibiotic cefuroxime axetil as the active ingredient, and an effective amount of a disintegrant to cause tablet core disintegration right after film coat rupture.

Three compartments make up the system. The immediate-release compartment has a compressed mixture of an active ingredient and one or more disintegration-capable polymers that, when exposed to water, would rupture to further degrade the already fragile extended-release compartment and, ideally, provide full drug release. A compressed blend of the active agent, a hydrophilic polymer that dissolves to weaken the structure of the extended-release compartment, and hydrophobic polymers that delay water penetration make up the second compartment, which is an extended-release compartment that is created by press-coating to largely enclose the immediate-release compartment. An instant-release compartment, which is made up of a compressed blend of an active agent and polymers and is created by coating to largely enclose the extended-release compartment, makes up the third compartment. This allows the active agent to be released prior to the first-order release.

2.3 Pulsatile transdermal delivery devices.

By stimulating the drug devices or reservoirs chemically or physically, pulsatile drug delivery systems control the pace at which the drug is released from the devices, resulting in periodic drug pulsations. A patent has been awarded to Clifton A. Baile et al. for a delivery system that uses an aperture to pulsatilely release the beneficial substance. Ashutosh Sharma et al. demonstrated pulsatile hormone administration from a pre-loaded integrated electrotransport patch. To administer gonadotropin-releasing hormone via a membrane, the system combines an integrated electrode assembly with an electrically assisted delivery mechanism. Dan Sibalis revealed the same kind of technology, an iontophoretic system that allegedly delivers a medicine in pulses via a patient's skin. It appears that Sibalis achieves the pulsatile delivery profile by altering the driving force that transports the medication through the skin, or the amount of current that is delivered to the skin. Numerous patents that offer pulsing transdermal medication delivery systems have been referenced in the literature. A potential method for delivering biologically active substances in a pulsatile pattern has been demonstrated via a medical device for pulsatile transdermal administration.

2.4 Pulsatile drug delivery using hydrogels.

A stimuli-sensitive hydrogel-based pulsatile drug delivery device is described by You H. Bae et al. The primary focus of this invention is on drug-loaded hydrogel delivery systems that, in response to internal or external stimuli like pH or temperature changes or chemical reactions, mechanically squeeze and release the pharmaceuticals. The impact of various hydrophilic/hydrophobic medications with their physicochemical characteristics on swelling/deswelling kinetics and pulsatile drug release from thermoresponsive poly(N-isopropylacrylamide) hydrogels was investigated in a similar work by D.C. Coughlan et al. The addition of the hydrophobic medications was shown to inhibit the rate of hydrogel swelling. In contrast to the unloaded system, the hydrophilic series accelerated the pace of swelling. The amount of swelling before the temperature change was always correlated with the size and velocity of hydrogel contraction.

Table 2: Diseases requiring pulsatile drug delivery

DISEASE	CHRONOLOGICAL BEHAVIOR	DRUGS USED
Peptic ulcer	In the afternoon and at night, there is a greater secretion of acid.	H2 blockers
Asthma	Attacks that occur at night or in the early morning	β2agonist, Antihistaminic
Antihistaminic diseases	When you sleep, your blood pressure is at its lowest, and when you wake up in the morning, it increases sharply.	Nitroglycerin, Calcium channel blockers, ACE inhibitors etc.
Arthritis	Morning ache and nighttime agony that becomes worse	NSAIDs, Glucocorticoids
Diabetes mellitus	A rise in blood sugar levels following a meal	Sulfonylurea, Insulin, Biguanide
Attention	An increase in afternoon DOPA levels	Methylphenidate
Hyper cholesterolemia	In general, the synthesis of cholesterol is higher at night than during the day.	HMG CoA reductase inhibitors(Sirisha et al., n.d.) [1] [3]

Table 3: Marketed technologies of pulsatile drug delivery

Technology	Mechanism	Proprietory name and Dosage form	API	Diseases
OROS®	Osmatic mechanism	Covera-HS ®: XL Tablet	Verapamil HCL	Hypertension
Three	Externally regulated Dimensional system printing®	Theirform®	Dicloenac sodium	Inflammation
CODAS®	Multiparticular pH dependent system	Verelan® PM : XL release capsule	Verapamil HCL	Hypertension
DIFFUCAPS ® system	Multiparticular Tablet	Innopran® : XL	Verapamil HCL Propranolol HCL	Hypertension
PULSINCAP ®	Rupturable system	Pulsincap®	Dofetilide	Hypertension(Sirisha et al., n.d.) [3]

3. Drug Release Mechanism of PDDS:-

3.1 Osmosis

Under some circumstances, the presence of water may cause the pharmaceutical molecule to create an osmotic pressure. A change in the solute's concentration across the semi-permeable barrier generates pressure. Due to their selective nature, semi-permeable membranes let water to pass through while mostly blocking solute molecules. The pressure used to halt solvent flow on the more soluble side is known as osmotic pressure. Therefore, osmosis is the process by which water moves from a region of greater concentration to one of lower concentration over a semi-permeable barrier.

3.2 Erosion

Less coating is used since the active substance will be released when the coatings decompose more gradually. Two distinct erosion mechanisms are used by pulsatile drug delivery systems to release medicines. Surface erosion and hydrolytic breakdown take place where the polymer and water come into close contact. Furthermore, as is frequently the case with hydrolytically degradable polymers,

the rate of water diffusion is greater than the rate of hydrolytic destruction. After then, the polymer membrane's bulk will rapidly come into contact with moisture and start to degrade. Unlike a solid polymer membrane that thins over time, the barrier maintains its dimensions while gradually losing solidity until it completely disintegrates. It mostly affects polymers that are acid-catalyzed, meaning that autocatalysis-based degradation may effectively break down the polymer from the inside out since the bulk of the polymer includes acid degradation products. The thickness of the membrane greatly affects the behavior of erosion because it regulates the amount of water and autocatalytic chemicals that are present in the membrane's interior. [7] [8]

3.3 Diffusion

Water is able to diffuse into the medication molecule. The medicinal ingredient interacts with the gastrointestinal system's liquids before diffusing outside through the delivery coat. [9].

4. Need For Pulsatile Drug Delivery

Because PDDS is required when the body's circadian rhythm is disturbed or when a chemical breakdown takes place in the stomach region, the release's lag time becomes important. Additionally, PDDS is required for targeted distribution to the exact area in the GIT (Gastrointestinal Tract) of a medicine that degrades via the first-pass effect, as well as localized drug delivery to produce the appropriate therapeutic response. It has been shown that PDDS provides a prospective benefit to patients with time-dependent illnesses where the medicine dose is crucial at a certain time, such as myocardial infarction, cancer, arthritis, stomach ulcers, asthma, and angina pectoris.

5. Classification of Pulsatile Drug Delivery[1] [9]

5.1 Based on stimuli-response pulsatile drug delivery:-

Drug distribution is aided by the stimuli-responsive systems' ability to react to physiologically produced impulses. In these systems, the medication is delivered after being stimulated by biological factors including heat and physiological reaction. It is of interest to design a stimuli-sensitive administration system that releases the therapeutic medication when certain enzymes are present. Stimuli-responsive pulsatile drug delivery is therefore a feasible alternative as it may be used as required.

5.1.1 Chemical stimuli-induced pulsatile release

The development of pH-responsive intelligent biomaterials that adapt to changing environmental conditions could be feasible. Local therapeutic delivery is made possible when the pH of the surrounding environment seems to be either basic or acidic.
Qu et al.'s most recent study examined the usage of N-carboxyethyl chitosan as an intravenous hydrogel for the treatment of liver fibrosis in conjunction with dibenzaldehyde-terminated poly (ethylene glycol) encased in doxorubicin. This study showed how changes in pH result in physicochemical changes that allow the structure of this polymer to expand and release the drug it contains. The well-known idea of forming fluorescent boronate nanostructures in doxorubicin for internal imaging and inhibiting malignant cell lines was developed by Li et al. When the pH was raised from 5.4 to 7.4, the biopolymers exhibited a fast-tempered emission of doxorubicin following a restricted release. A separate method was used by a team investigating sodium bicarbonate in PLGA empty microspheres. At lower pH values, bicarbonate breaks down carbonic acid to form carbon dioxide and water. This increases gas pressure and makes it possible to breach the PLGA cover, revealing the antibiotics within. Further studies have concentrated on the sensitive effects of raising pH, focusing on areas such as the small intestine. For the drug to be released at pH 8.0, Hydrogels containing blank particles trapped inside acrylamide polymers were produced by Pafiti et al. Since the colliding particles were dissolved at a higher pH, the pH-sensitive material may preserve its natural structural properties at the stomach's pH of 4 and improve drug release. Furthermore, because polymeric biomaterials may be made in a wide range of shapes and forms, these systems can distribute through a number of routes, including parenteral, intracoronary, intramuscular, oral, and epidermal. When pH-sensitive equipment is used for distribution or installation, there is a chance of off-delivery. More research, development, and innovations in pH-responsive polymers are made feasible by resolving these issues and strengthening the benefits that are already there. This makes it easier to distribute drugs. Some preparations also applied an intermediate acidic layer containing organic acids, such as fumaric acid, citric acid, succinic acid, and malic acid, between the first and second layers for time-controlled pulses because the presence of acids between the membranes delays the dissolution of the enteric polymer in the inner layer.

The enteric coating membrane was included into the inner layer to facilitate the release of the drugs in the lower intestine.

5.1.2 Thermo-responsive pulsatile discharge

One often used trigger signal for pulsatile discharge is temperature. The body temperature often deviates from the physical temperature (37 °C) when pyrogens or diseases are present. This deviation from the typical range serves as a trigger for many temperature-responsive systems, causing them to release therapeutic chemicals.

5.1.3. Thermo-responsive hydro gel systems.

Thermosensitive gels undergo variable volume transitions in response to temperature fluctuations. These gels collapse due to a linear polymer's lower critical solution temperature (LCST). Because it changes volume, this characteristic can produce a squeezing hydrogel by encasing the hydrogel inside a rigid capsule. For example, temperature-sensitive hydro gel's reversible volume change enables on-and-off-release. Thermoresponsive swelling and deswelling phases are intermittent in PIPAAm cross-linked gels; they expand below 32 °C and contract above it. The end-functionalized PIPAAm was converted into block copolymers using lipophilic polymers. Micellar structures with a core-shell structure were generated via block composites in aquatic solutions below the PIPAAm transition temperature. This approach releases medication when the polymer enters an expanding or non-expanding phase due to inflammatory stimulation, chemical interaction with the membrane, or a change in pH.

5.2. Time-controlled pulsatile discharge systems

5.2.1. Osmosis-based capsular structure

The osmotic process is a capsule with a semi-permeable membrane. The capsule contained the medication formulation, an osmotically active ingredient, and an indissoluble stopper. This capsule's semi-permeable membrane allowed water to enter when it came into touch with body fluids, which led to pressure that finally pulled the indissoluble plug out. This method makes use of a capsule with a semipermeable membrane covering it.

When the capsule shell comes into contact with gastrointestinal fluids, the semipermeable barrier permits gastric fluid to enter. The plug's expansion results in osmotic stress. Lag time is the time it takes for a membrane to rupture; the membrane explodes when the strain exceeds its tensile strength. The drug is released when the plug is ejected after a brief delay. A robust gelatin capsule containing paracetamol, sugar (sorbitol), an osmotic regulator, and sodium dodecyl sulfate, a releasing accelerator, was developed by Barzegar-Jalali associates.

5.2.2. Expandable orifice-based system

An osmotically controlled capsular method was used to provide the liquid drug. The medication is absorbed into high porosity molecules shortly after the barrier coat has been dispersed throughout the liquid. These molecules then release the drug through an aperture of a semi-penetrable compartment that is supported by a growing osmotic coat. This approach combines the advantages of a long half-life and extended discharge. Liquids can be used to deliver indissoluble drugs, polypeptides, and polysaccharides. The wall of the capsule stretches as osmosis progresses because of the increased internal tension. Therefore, when the flexible walls are stretched past a certain point, the aperture achieves the correct size and discharges the material at the specified pace. Elastomers like styrene-butadiene copolymer have been strongly suggested. Depending on the barrier layer and semi-permeable membrane thicknesses, pulsatile discharge happens after lag times ranging from 1 to 10 hours.

5.2.3. PORT system

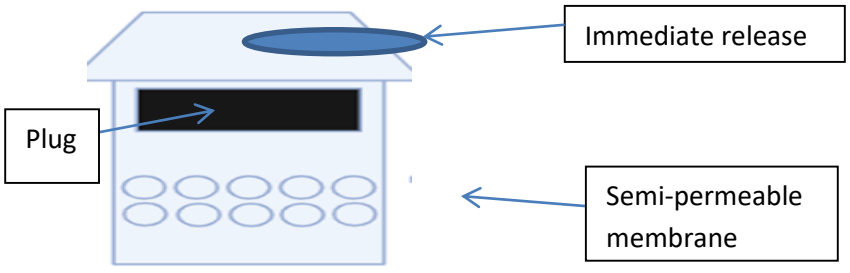

Figure 4: Port System

The capsule consists of an insoluble plug that contains an osmotically active material and the drug. The indissoluble drug was released as a consequence of stress caused by the semi-permeable barrier

of this capsule, which let water in when the dissolving agent came into contact with it. Methylphenidate, which is used to treat attention deficit hyperactivity disorders (ADHD), was distributed using such a device using a method known as the pulsatile port system.

5.3. Pulsatile system with soluble or erodible barrier coatings

5.3.1. Tablets*:* Since the top coat and interior body are crushed into a single compressed layer, coating solutions are not needed. The inner body is simultaneously prepared using substances that are discharged into the intestinal area but insoluble in the stomach medium. This might be achieved by using a cellulose derivative. Two advantages of press-layered pulsatile drug delivery systems are their ability to preserve acid-labile drugs and their low production costs. This method's main flaw is the massive quantity of coating ingredients needed.

5.3.2. Multi-layered tablet*:* A tri-coated tablet having two drug-carrying coats separated by a drug-free gellable polymeric barrier coat can create two pulses. These three coated tablets have the top portion exposed while the other three sides are laminated with impermeable ethyl cellulose. When the uncoated surface comes into contact with the dissolving medium, the initial dosage that was absorbed into the top coat is immediately released. The subsequent pulse is extracted from the bottom coat following the erosion and disintegration of the HPMC layer**.**

5.3.3. Clock-time system: In the time-based system, a solid-state pharmaceutical state is encased in a liquid dispersion delivery mechanism. At 75 °C, beeswax, a water-hating surfactant coat, diffuses across the core. The application of a water-soluble coat enhances adherence to the core coat.

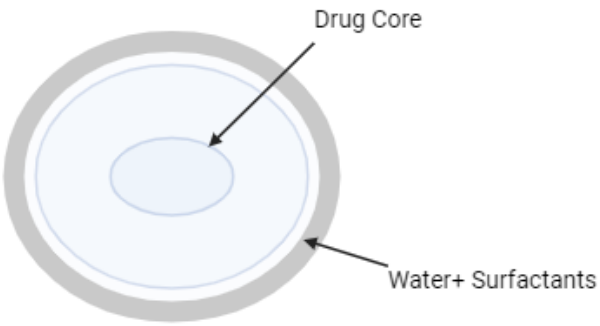

Figure 5: Clock time system

5.3.4. Chronotropic system*:* A drug-containing core in the chronotropic system is covered by water-loving swellable HPMC, which causes a delayed release. If the small intestine transit time remains constant, an outer enteric layer can provide a colon-target discharge by avoiding the difference in empty stomach length. The HPMC viscosity and thickness classes address the delay time. Both in-vitro and in-vivo delay periods are significantly influenced by the quantity of hydrophilic retarding polymer used. Poonuru et al. developed and evaluated a bimodal chrono-controlled drug delivery system for methylphenidate hydrochloride. The core pills were formulated using diluents (microcrystalline cellulose PH 102, Ludipress) and the super disintegrant Kollidon CL SF (4% and 8%). Batch F10 generated the best release, with 70% HPMC E50 at 70%, 60% released gradually over 4 hours, and 40% released suddenly in a burst at 5 hours. The greatest results, which matched circadian fluctuations in the disease state, were obtained with the A1 formulation that included Cellactose-80 as a diluent.

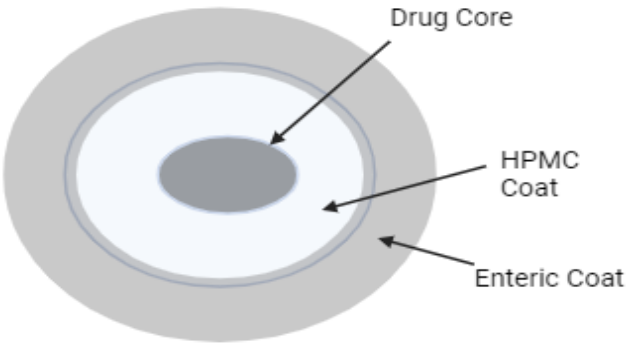

Figure 6: Chronotropic system

5.3.5. Capsule-based system*:* Typically, the exterior body of such devices consists of an indissoluble capsule that contains a drug and a plug. Over time, the plug separates due to disintegration and swelling. The plug grows and finally pushes out of the capsule when it comes into touch with stomach contents or a dissolving solvent. In addition, the drug is released rapidly. By altering the plug's placement and diameter, the delay time may be changed.

5.4. Multiparticulate/multiunit system

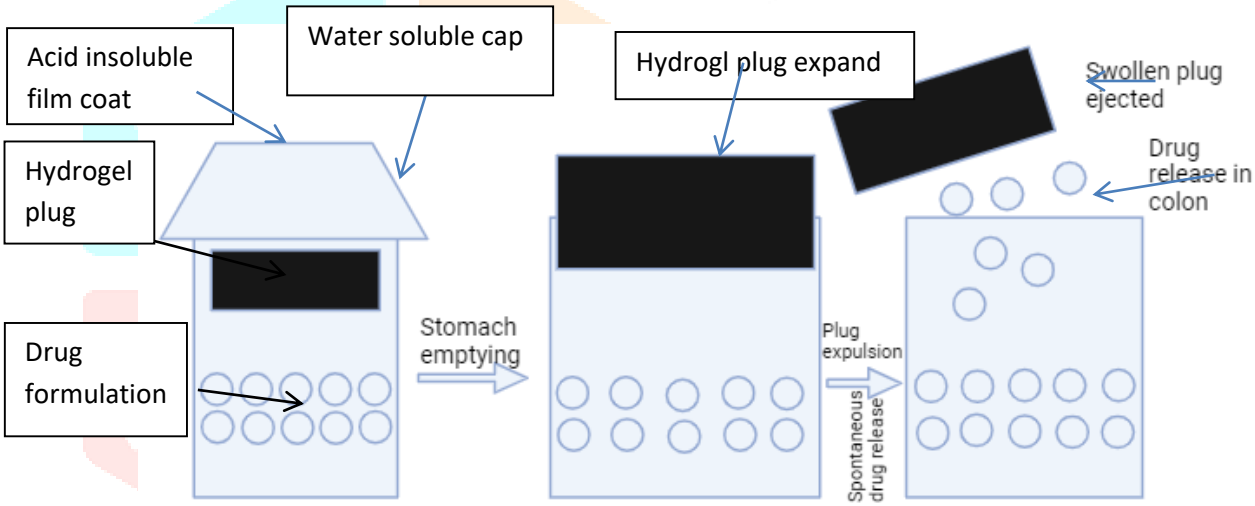

Figure 5**:** single unit pdds

5.4.1 Pulsatile delivery by a change in membrane permeability:

The quaternary ammonium groups connected to the counterion in the acrylic polymer affect the permeability and water absorption properties of the releasing medium. These features are beneficial for the timed release of medications in the intestinal area. Eudragit RS and RL are the best choices for acrylic polymer. A positively charged quaternary ammonium functional group and a negatively charged hydrochloride are its counterions. The water-soluble ammonium group illustrates how interaction with water functional groups altered the polymer, enhancing water penetration into the drug core and permitting controlled distribution through the use of a certain lag time. Che et al. developed a biomimetic and bioactive scaffold that was loaded with teriparatide pulsatile delivery in order to regenerate osteoporosis both locally and systemically. Osteoporosis, which can lead to osteoporotic fractures and even death, is one of the challenging problems of aging. As a result, teriparatide is considered a necessary medication for treating osteoarthritis; yet, its therapeutic uses are restricted due to its adverse effects. Conventional drug delivery systems do not exhibit sensitive and short-term medication release. Thus, a biomimetic and bioactive scaffold containing teriparatide was developed for on-demand drug release. The study found that the pulsatile release of teriparatide from the smart system is responsible for osteoporotic bone defects, their repair, and their potent antiosteoporosis action. Teriparatide pulsatile injection employing biomimetic and bioactive scaffolds is a feasible approach that might be commercialized for the treatment of osteoporotic fractures, according to the study's final result.

5.4.2 **Pulsatile system with a rupturable coating:** A reservoir consisting of swelling polymer, rupturable permeable polymer covering, and active medicinal ingredients makes up the pulsing system with rupturable coatings. The water-insoluble porous polymer that is externally coated in this way allows water to enter the tablet core. The infiltrating water causes the polymer in the tablet core to expand; when the pressure inside the system increases, the polymer bursts, resulting in the release. The rapid release of drugs from the polymer coating requires pressure, and agents that cause gas production, swelling, and osmotic pressure can aid in this process. Liu et al. examined the effects of pulsatile and sustained-release coating on multiunit tablets containing isosorbide-5-mononitrate (5-ISMN) for the treatment of angina pectoris.

5.4.3 **Osmotic-based rupturable coating system:** The osmotic-based rupturable coating technique focuses on the osmotic and swelling processes. This system is composed of a pharmaceutical core, a low-density material, a disintegrating agent, and a cellulose acetate covering. When water penetrates through the core and raises internal pressure, the tablet's covering bursts, releasing the drug. Hung et al. reported omeprazole and propranolol hydrochloride utilizing a multiarticulate pulsatile delivery system that incorporated Eudragit RS (a rupturable controlled release membrane) and sodium chloride (as an osmogent). The study showed that using the extrusion/spheronization technique in the presence of osmogent was the most efficient way to create drug/osmogent-containing pellets. The other two model active components were more soluble in water. The 4% osmogen created a lag time of 0–12 hours by controlling the membrane thickness, and the plasticizer concentration resulted in a pulsatile profile of propranolol hydrochloride. Therefore, it was concluded that a pulsatile delivery system that is triggered by osmotic pressure can also be employed for chronotherapy in a clinical environment.

5.5 Externally regulated pulsatile delivery system

5.5.1 Pulsatile delivery that is electroresponsive: Remote-controlled drug delivery systems include pulsatile distribution devices that react to electricity. This system administers medication using external stimuli and triggers, such as near-infrared lights, ultrasound, magnetic fields, electric fields, and radiofrequency. The electric field provides a precise and effective stimulation to the delivery system by altering the voltage supply. Hydrogel-based formulations, i.e., polymeric implants, have shown remarkable biocompatibility with respect to temperature, pH, and electric field. In reaction to these outside stimuli, the hydrogel-based polymeric implants provide a pulsatile release. Kagatani et al. evaluated the electroresponsive pulsatile insulin depot administration from poly (dimethyl aminopropyl acrylamide) (PDMAPAA) gel in rats. After being injected into an electro-responsive PDMAPAA gel, insulin was given to rats as a depot under their skin. The gel caused a pulsating drop in plasma glucose levels when the current was kept constant at 1.0 mA (0.36 mA/cm2). It was shown that the gel released 0.12% of the insulin after these two stimulation, indicating pharmacological bioavailability. In the end, the electro-responsive PDMAPAA gel migrates throughout the gel network with the assistance of the electro-kinetic migration of solvated insulin and water molecules, releasing insulin.

5.5.2 Ultrasonically stimulated pulsatile release

Ultrasound stimulation facilitates penetration. It provides controlled drug absorption through the skin, blood vessels, lungs, and intestines. The polymer in pulsatile formulations broke down when exposed to ultrasonic vibrations, enhancing medication release through both initial burst and sustained release. Additionally, the cavitation process brought on by ultrasonic irradiation facilitates the pulsatile drug dispersion from the polymer-based formulations. According to Emi et al., calcium crosslinked alginate hydrogel loaded with macromolecules (chemotherapeutics, dextran, and protein signaling factor) allows for sequential and pulsatile delivery patterns through signal and multi-pulse exposures. Due to a single-pulsed ultrasonic treatment that caused molecular release and gel erosion, it was challenging to administer therapeutics from the gels without causing damage or overheating them. Nevertheless, despite

maintaining gel disintegration and reducing temperature rises, more therapeutic material was released after multi-pulse ultrasonic exposures. The results of the study suggest that ultrasonically responsive polymeric hydrogel might be used to improve and regulate complicated therapeutic delivery techniques in the treatment of cancer.

5.5.3 Magnetically induced pulsatile release

The magnetically induced pulsatile delivery method uses an oscillating magnetic field to control the dispersion of active pharmaceutical ingredients (API) from polymer-based formulations. Magnetite, nickel, iron, and cobalt are integrated magnetic minerals that function as magnetic carriers and regulate drug administration using polymeric pulsatileformulations. Magnetic carriers are water soluble, biocompatible, non-immunogenic, and non-toxic to the human body. Because the magnetic carriers slow down the medication's travel to the stomach and intestine while being impacted by the external magnet, the absorption of the medicine is changed after oral administration. The outcome is a pulsating delivery. Emi et al. have developed and evaluated pulsatile devices containing chemotherapeutic medications using magnetically assisted hydrogel compositions. The study found that melanoma cells reacted more favorably to the pulsatile pattern. Tests also showed that characteristics like drug duration on periods, pulse widths, and release rates might be employed to improve delivery patterns. It shown that magnetically sensitive biphasic ferrogels may provide pulsing mitoxantrone delivery patterns that resemble those evaluated in the laboratory. The pulse scheduling was controlled by selecting the magnetic field stimulation timing and duration. These findings illustrated the possible advantages of chemotherapeutic administration behavior based on pulsatile. It also suggests that magnetically assisted hydrogel formulations may be helpful tools for improving pulsatile chemotherapeutic distribution patterns in clinical situations. [6] [9]

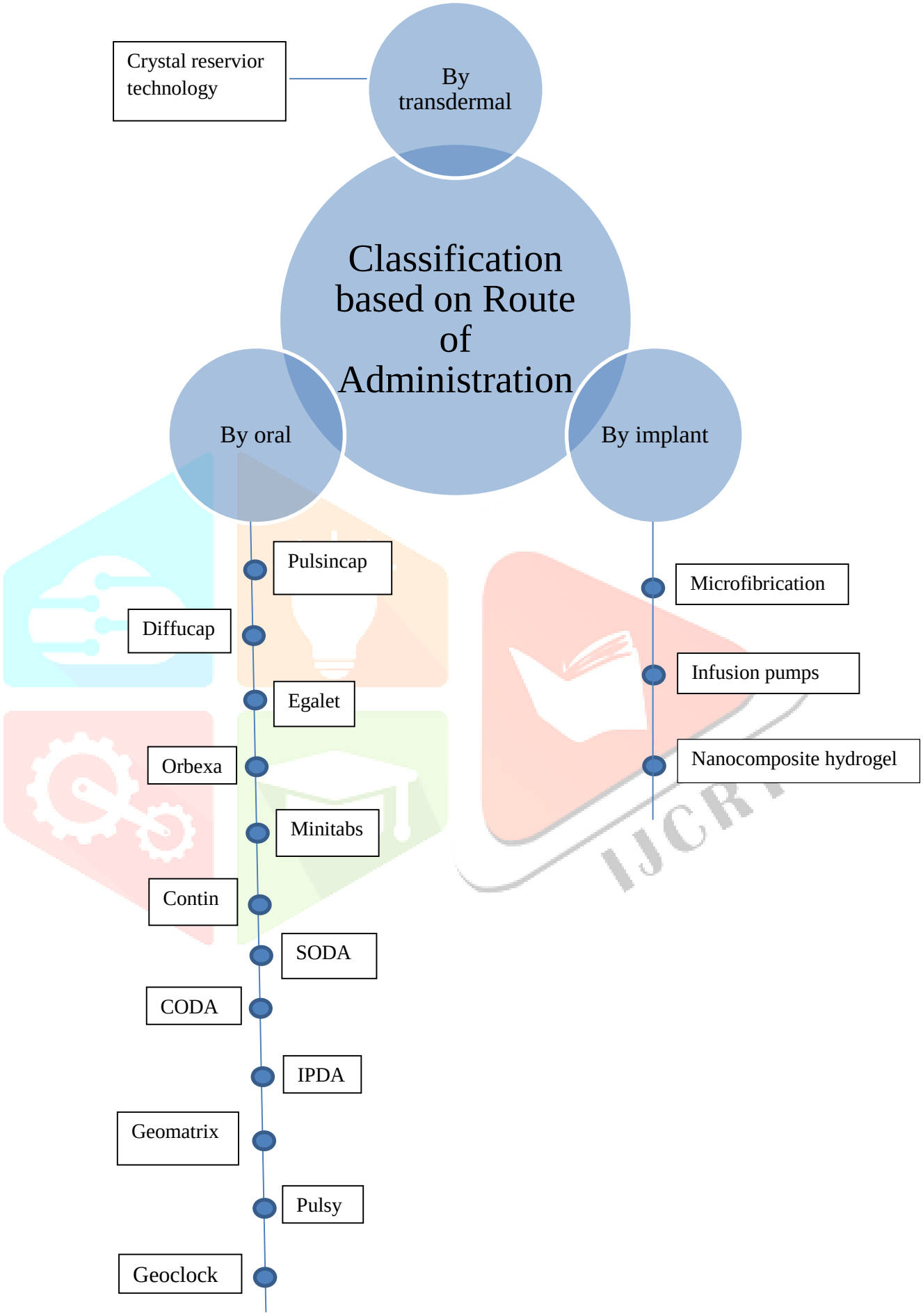

Fig. Classification based on route of administration. [10]

6. Oral Route:

6.1 Pulsincap® Technology

R.R. Scherer International Corporation (Michigan) created Pulsincap. The non-disintegrating half-capsule body of this device is covered with a water-soluble cap and has a hydrogel plug sealed at the open end. To prevent the issue of variable stomach emptying, an enteric polymer is applied to the whole unit. This capsule expands as it comes into touch with the dissolving fluid, and then, after a little delay, the plug forces itself out of the capsule, releasing the medication quickly. By adjusting the plug's dimensions and location, the time lag may be managed. Effervescent agents or disintegrants can be added to water-insoluble medications to guarantee a spontaneous release. Congealed melted polymers (saturated polyglycolated glycerides), erodible compressed polymers (hydroxypropylmethylcellulose, polyvinyl alcohol, and polyethylene oxide), insoluble but permeable and swellable polymers (polymethacrylates), and enzymatically controlled erodible polymers (pectin) make up the plug material. [10] [11]

6.2 Diffucaps® Technology

created in the USA by Eurand Pharmaceuticals Ltd. Diffucaps is a multiparticulate bead system that regulates the rate of drug release by combining many layers of drug, excipients, and a functional polymer membrane. Capsules can be filled with Diffucaps beads, which have a diameter of less than 1.5 mm. The organic acid or alkaline buffer layer on the beads helps regulate a drug's solubility by establishing the ideal pH microenvironment for medications that are poorly soluble in physiological fluids, environments with a pH higher than 8.0, or in the intestinal pH. To improve bioavailability by keeping the medication in its amorphous form, the beads may also contain a solid-solution of the drug and crystallization inhibitor.

Diffucaps ® has the following benefits:

- It is perfect for medications that are poorly soluble in physiological fluids, settings with a pH higher than 8.0, or lower intestinal pH.
- It can combine many medications and/or release profiles in a single dose form.
- Able to reduce the impact of food. [10]

6.3 CONTIN ® Technology

A product of Purdue Pharma. Closer control over the amount of medicine delivered into the bloodstream is made possible by this technology, which also helps patients by lowering the number of daily dosages they must take, improving illness management (especially at night), and minimizing undesirable side effects. A cellulose polymer and a non-polar solid aliphatic alcohol that has been optionally substituted with an aliphatic group can form molecular coordination complexes by solvating the polymer with a volatile polar solvent and reacting the solvated cellulose polymer directly with the aliphatic alcohol, ideally as a melt. Due to its consistent porosity (semi permeable matrixes), which may be adjusted, this compound is useful as a matrix in controlled release formulations. Theophylline, morphine, aminophylline, and other medications now come in tablet form because to this technology. [10] [12]

6.4 CODAS® (Chronotherapeutic oral drug absorption system)

CODAS® technology was created by Elan Corporation in the United States. The amount of non-enteric release-controlling polymer added to drug-loaded beads causes a delay. A blend of water-soluble and water-insoluble polymers makes up the release-controlling polymer. The medicine diffuses through the coating's pores when the water-soluble polymer gradually dissolves when gastrointestinal tract water comes into touch with the polymer-coated beads. The drug's regulated release is maintained by the water-insoluble polymer's continued barrier function. A controlled onset, an extended release delivery system, a delivery profile that complements the circadian pattern, a rate of release that is essentially independent of pH, posture, and food, "sprinkle" dosing—opening the capsule and sprinkling the contents on food—a decrease in the effective daily dose and drug exposure, gastrointestinal tract targeting for a local effect, and a reduction in systemic exposure to achieve a target profile are some of the benefits of the CODAS technology.

6.5 Egalet® Technology

Developed in Denmark by Egalet Ltd. The active medication is positioned between the two lag plugs that make up the system's impermeable shell. There is a lag period because the medicine is released after the inert plugs have corroded. The plugs' length and composition can be used to adjust the release time. This technology exhibits medication release with erosion control. The plugs' matrix is composed of a blend of pharmacological excipients, including polymers like polyethylene oxide (PEO), while the shells

are composed of slowly biodegradable polymers (such ethylcellulose) and plasticizers (like cetostearyl alcohol). This method is used in the development of several opioid medications. [10] [13]

6.6 IPDAS® (Intestinal protective drug absorption system)

A novel oral drug delivery method that works with gastrointestinal (GI) irritant medications, such as the family of non-steroidal anti-inflammatory medicines (NSAIDs). A large number of controlled-release, high-density beads are crushed into tablets to produce the IPDAS technology. Regardless of the eating condition, an IPDAS tablet dissolves and releases drug-containing beads in the stomach after consumption. These beads then gradually and carefully move into the duodenum and other parts of the digestive system. The polymer system utilized to coat the beads and/or the micromatrix of polymer/active ingredient created in the extruded/spheronized multiparticulates regulate the release of the active ingredient. The multiparticulate quality of the formulation, which guarantees broad dispersion of the irritating medication throughout the gastrointestinal system, is what gives this technology its intestinal protection. [14]

6.7 Geoclock®

manufactured by SkyePharma. It comes in the form of press-coated tablets with a chronotherapy focus. In order to achieve a pH-independent lag time before core medication administration at a pre-established release rate, geoclock tablets include an active drug inside an outer tablet layer made of a combination of hydrophobic wax and brittle material. With this dry coating method, the inside tablet is released first, while the outer shell progressively breaks down, enabling the timed release of both delayed release and instant release active cores. Apart from controlled release, Geoclock technology may also be used for multiple pulse drug delivery, which delivers doses of a medicine at predetermined periods throughout the day, and for better release colonic drug delivery. [15]

6.8 Geomatrix®

created in the USA by Skye Pharma Plc. One or two impermeable or semi-permeable polymeric coatings (films or compacted barriers) are placed to one or both bases of the hydrophilic matrix core of the tablet, which contains the active component and serves as a surface-controlling barrier. Geomatrix technology has several advantages, including the ability to produce two different drugs at different rates from a single tablet at the same time, reproducibility, controlled release of poorly soluble drugs, timed release, pulsed release, and safety of use. It can also be easily integrated into a production line. Nifedipine, Diclofenac sodium, and Diltiazem hydrochloride are a few medications that are sold using this technology. [13] [16] [17]

6.9 Diffutab®

Pulsed delivery that is focused and maintained can benefit from this technique. By combining hydrophilic polymers and waxes, the Diffutab technology regulates medication release by causing a matrix tablet to erode and diffuse. Diffutabs are especially helpful for goods that have large dosages. Both soluble and insoluble materials can use this method. [10]

Advantages of Diffutabs

- The active medication and water-soluble particles are combined in matrix tablets.
- Supports once-daily, sustained-release dosage.
- ideal for heavy drug loading

6.10 PulsysTM

MiddleBrook Pharmaceuticals developed this system, which allows for the prolonged release and absorption of a drug and allows for the pulsatile delivery or delivery of certain drugs in rapid bursts. The system was designed with the rationale that antibiotics are more effective against bacteria that grow quickly, according to reports. The administration of a pulsatile system is more effective in this situation because the regular release of increased antibiotic pulses prevents the bacteria's defense system from going into a dormant state, whereas bacteria respond to immediate release antibiotics by going into a dormant stage. Preclinical research has demonstrated that the pulsatile method of antibiotic delivery works better.

6.11 SODAS® (spheroidal oral drug absorption system)

The Elan Corporation developed it. The uniform spheroidal beads, which have a diameter of 1-2 mm, comprise the multiparticulate drug delivery system. The medication is first administered to an inert core in each bead, which is followed by many layers of soluble and insoluble polymers mixed with other excipients to create the rate-controlling layer. Diffusion is how the drug is released from these beads. The soluble polymers break down inside the GI tract, creating holes in the outer membrane. The medication is subsequently dissolved by fluid that penetrates the beads' center. The resulting solution

allows the in vivo dissolution and absorption phases to be prolonged by diffusing out in a controlled, predefined way. Excipients can be used to control the drug's immediate environment within the seed core, ensuring the best possible stability and solubility. To create the final dose form, these controlled-release beads can be compacted into a tablet or packed into a capsule. The SODAS® technology, which is based on the creation of controlled release beads, is distinguished by its intrinsic adaptability, which makes it possible to create personalized dosage forms that directly address the requirements of each drug candidate.

6.12 Orbexa®

Aptalis Pharmaceutical Technologies is the developer. It is made up of small, cylindrical tablets that measure 2 mm by 2 mm and are covered with a functional membrane that regulates the pace at which the medicine is released. Gel-forming excipients that regulate the rate of medication release are present in them. To further regulate the discharge rate, more membranes might be added. Because the tablets are packed into capsules, several medications and/or release profiles can be combined in a single dose form. Before being further coated, minitabs can be prepared as matrix tablets. Minitabs offer the following benefits: they are ideal for high drug loading, combine the ease of tablet formulation with the complexity of multiparticulate systems, and may be used as a sprinkle for elderly and pediatric patients who have trouble swallowing tablets. [16] [17]

7. By implant:

7.1 Microfabrication

These devices have tiny medication reservoirs that are sealed off from the outer world by a thin membrane. A tiny coating of gold serves as the active silicon-based microchip membrane. The voltage must be provided in order for the medication to be released. The electrochemical breakdown of thin anode membranes enclosing microreservoirs containing solid, liquid, or gelled substances is the basis of the release mechanism. This is a solid-state silicon microchip that can release one or more chemicals under regulated conditions as needed. A regulated, pulsatile release of chemical compounds was shown utilizing a prototype microchip in a release investigation that used saline solution and gold as a model electrode material and release medium.

7.2 Magnetic nanocomposite hydrogel

Temperature-responsive hydrogel magnetic nanocomposite was employed for remote-controlled pulsatile drug administration. Superparamagnetic Fe3O4 particles and a model medicine were added to negative temperature-sensitive poly (Nisopropyl Acrylamide) hydrogels to create nanocomposites. When a high frequency alternating magnetic field is introduced, the beads in the matrix oscillate, producing compressive and tensile pressures. Additionally, when the temperature of the hydrogel rises, the gel collapses more quickly. This then serves as a pump to force more of the drug molecule out of the matrix, resulting in pulsatile drug release from the hydrogel nanocomposite on demand. It is also possible to add magnetic particles such as steel, cobalt, nickel, iron, and magnetite. [17]

8. Conclusion

The pulsatile drug delivery system's recent surge in popularity can be attributed to its ability to release the medication into the patient's body at the appropriate time, location, and dose. The development of alternative formulation strategies—such as external stimulation, rupturable membrane, single unit, and stimuli-responsive—can improve the conventional system and plan its pulsatile release while taking patient demands into account. It should be mentioned that these drug delivery methods are still in their infancy and that further research is required before they can be applied as practical clinical substitutes. The research that is now accessible makes it abundantly evident that circadian rhythms have become increasingly important in the fields of physiology, pharmacology, molecular biology, and health sciences in recent years.

In the future, novel strategies like the use of hydrogel and transdermal systems in chronopharmaceutics will undoubtedly enhance patient outcomes and maximize disease treatment. Pulsatile medication administration, which is regulated by the body's circadian rhythm and releases the medicine after a certain lag period, can successfully solve this issue. The development of a pulsatile drug delivery system that may successfully treat illnesses with nonconstant dosage regimens has advanced significantly. A bright and optimistic future is undoubtedly ensured by the numerous exciting technologies being developed and introduced to the market.

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