IJPSR (2023), Volume 14, Issue 1 (Review Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 10 May 2022; received in revised form, 29 June 2022; accepted, 01 August 2022; published 01 January 2023

PULSATILE DRUG DELIVERY SYSTEM- A SYSTEMATIC REVIEW

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Keywords:

Lag time, Pulsatile drug release, Rupturable coating

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ABSTRACT: Conventionally, drugs are released abruptly or comprehensively. But, in current years, pulsatile drug release systems (PDRS) are ahead raising attention. From PDDS, the drug is liberate quickly after a well defined insulate-time, could be helpful for many medicines or treatments. It can be labeled in single and a couple of-pulse structures. Other structures consist of a drug-enclosed core, enclosed by means of a swelling layer and an outer layer is insoluble, however coating with semipermeable polymer. The lag time earlier to the rupture is specifically controlled via: (i) the penetration and mechanical houses of the coated polymer and (ii) the behaviour of swelling depend on the swelling layer. As is within the residing frame frequently observed that, many fundamental capabilities are regulated with the aid of brief or pulsed launch of bioactive substances at a precise site and time. Therefore, it is miles grave to expand novel drug transport systems to attain pulsed launch of a sure amount of medicine. It is a good way to imitate the dwelling system's feature whilst reducing undesirable side results. Particular interest has been given to the thermally receptive poly (N-isopropyl acrylamide) and its imitative hydrogels. Pulsatile drug transport is a machine that, by means of handing over drug at the right vicinity, right amounts and in proper time, grips suitable assures of benefit to the patients affected by continual problems like high blood pressure, allergies, arthritis.

INTRODUCTION: Oral drug delivery is the top zone of the total drug transport market. It is the in particular preferential route for drug management. The oral controlled-release systems show a distinctive model of drug liberate in which the drug concentration is sustained in the curative window for an extended period, thus ensuring sustained therapeutic action. In certain conditions, this release pattern isn't always appropriate that insists release of a drug after a lag time.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.14(1).129-41

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.14(1).129-41

The pulsatile system is in advance of quite a few attention, as the drug is launched entirely after described insulates time **Fig. 1**. PDD is a website online and time-specific drug shipping, as a consequence imparting spatial and chronological shipping and increasing patient fulfillment.

Pulsatile drug transport is defined because of the fast and fleeting launch of a certain quantity of molecules within a tiny term immediately after a predetermined duration, *i.e.*, lag time or these systems have an unusual mechanism of handing over the drug quickly and completely after an insulate time. Such a release model is called pulsatile release [1-4]. The human body shows endogenous circadian rhythms synchronized by the master circadian clock, the suprachiasmatic center.

Chronopharmacotherapy of diseases (myocardial infarction, bronchial asthma, rheumatic disease, angina pectoris, ulcer, and hypertension) that explain circadian rhythm in their pathophysiology and management of such diseases entail PDDS, by which drug is released quickly and entirely as a pulse after insulate time [5-7]. Many other situations require pulsatile releases, like many frame capabilities that trail circadian rhythms, consisting of secretion of hormones [along with luteinizing hormone, follicle stimulating hormone, luteinizing hormone-releasing hormone, progesterone, and estrogen], acid secretion in the gastric emptying, stomach and GI blood transfusion. Drugs that produce biological lenience insist on a system that will stop their continuous occurrence at the bio phase, which tends to decrease their therapeutic effect.

The lag time is essential for pills that undergo degradation in gastric acidic medium and infuriate the gastric mucosa or persuade nausea and vomiting. Targeting a drug to a distal organ of the gastrointestinal tract, like the colon, wishes that the discharge is avoided in the two-1/3 part of the GIT. Drugs that endure first-pass metabolism, resulting in abridged bioavailability, changed steady-state levels of drug and metabolite. Possible food-drug interaction needs to be delayed release to the extent of potential [8-10]. The entire above attribute can be taken into a report in designing a delivery system that shows pulsatile release distinctiveness and discharges the drug in a programmed fashion at an exacting website. There are abundant benefits of PDDS. These are:

- ✓ These systems can be used for extensive daytime or night time action.
- ✓ They reduce the cost, dose frequency, and dose size, finally reducing side effects, thereby improving patient fulfillment.
- ✓ Drug adapts to suit circadian rhythms of body purpose or illness.
- ✓ Drug targeting to a definite site, like the colon.
- ✓ They defend mucosa from infuriating drugs.
- ✓ Drug loss by extensive first-pass metabolism is prohibited [11].
- ✓ They provide steady drug levels at the site of action and stop the peak-valley fluctuations.

Disadvantages:

- ➢ Small drug loading capacity and incomplete release of the drug.
- ➢ Numerous manufacturing steps.
- ➢ Lack of manufacturing reproducibility and efficacy.
- ➢ Higher cost of production.
- ➢ Trained/skilled personal needed for manufacturing.

The focus of the present review is primarily on the pulsatile drug delivery methodologies and the upcoming technologies being exploited in new technique development.

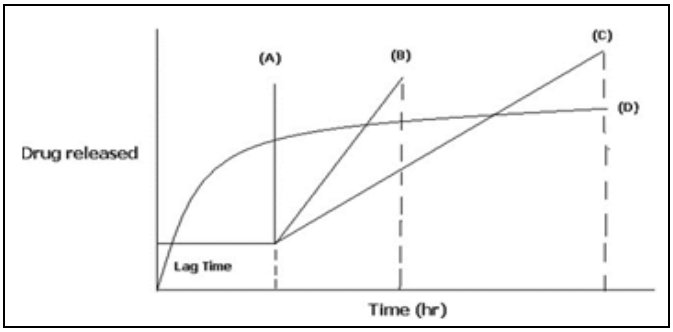

FIG. 1: SCHEMATIC REPRESENTATION OF DIFFERENT DRUG DELIVERY SYSTEMS, WITH (A) SIGMOIDAL RELEASE AFTER LAG TIME, (B) DELAYED RELEASE AFTER LAG TIME, (C) SUSTAINED RELEASE AFTER LAG TIME, AND (D) EXTENDED-RELEASE WITHOUT LAG TIME. [Reproduced from: Jain D., Raturi R., Jain V., Bansal P., Singh R. Recent technologies in pulsatile drug delivery systems. Biomatter. 2011; 1: 57-65.]

Chrono Pharmacotherapy

The Phrase Chronopharma: Celtics includes two words Chronobiology and Pharmaceutics. Chronobiology is the cram of biological rhythms and their mechanisms. A chronotherapeutic drug shipping machine is a drug delivery device based on the frame's biological rhythms. A chronomodulated machine is also recognized as pulsatile device or sigmoidal release system. There are 4 styles of mechanical rhythms in our body, which manage ordinary and disease-associated body structures of the body **Fig. 2**.

They are:

a) Circadian: The Oscillation completed in 24 hrs.

b) Ultradian: The Oscillation completed in a of shorter duration i.e. less than 24 hrs.

c) Infradian: The Oscillations longer than 24 hrs.

d) Seasonal: In the short winter days, seasonal affected disorder reasons melancholy in prone people. Out of four biological rhythms, circadian rhythm is the main rhythms in the body which maintains all the physiological, chemical, biological and behavioral processes [12-14].

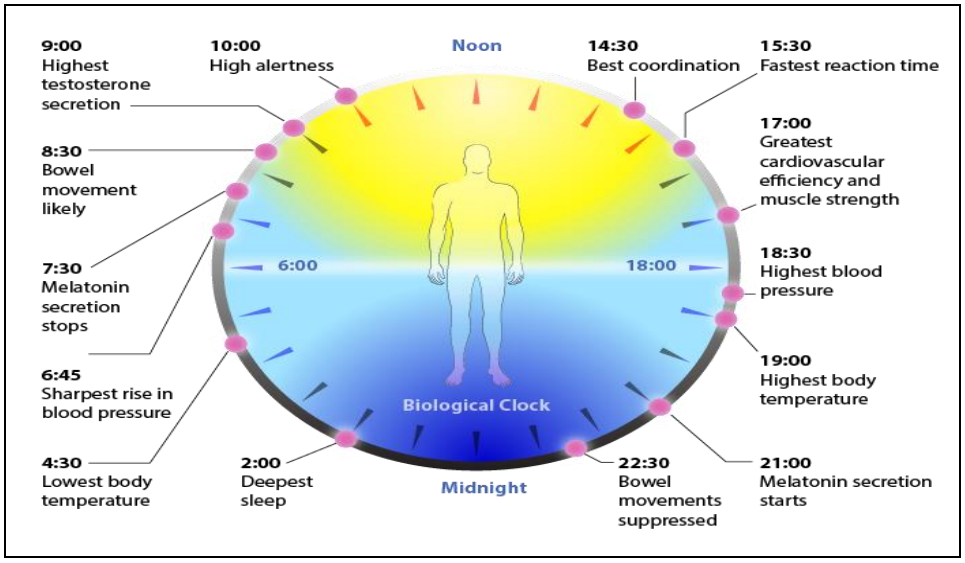

FIG. 2: CYCLE OF CIRCADIAN RHYTHMS. [Reproduced from: https://cpapvictoria.com.au/blog.]

Necessitate of Pulsatile Drug Delivery Systems:

- ✓ Numerous body functions follow circadian rhythm, *i.e.*, their action increases or decreases with time. Numerous hormones in the body prove daily in addition to timely fluctuations of their blood ranges. Circadian outcomes are also experiential in case of pH and acid secretion in gastric emptying, stomach and GI blood transfusion.
- ✓ Acid secretion, cholesterol synthesis, gastric emptying and GI blood transfusion may change with circadian rhythm.
- ✓ Chronopharmacotherapy of illnesses that explain circadian rhythms of their path body structure.
- ✓ Lag time is important for the ones tablets go through acidic degradation that worsen the gastric mucosa or results in nausea and vomiting.
- ✓ Targeting a drug to distal organs of GIT like the colon the drug release ought to be prohibited in the upper two-1/3 portion of the GIT.
- ✓ Drugs suffer tremendous first-pass metabolism that is simply given by PDDS.
- ✓ Drugs create biological lenience due to incessant exposure of drugs in the body. This system lenience by giving insulates time [15-17].

Mechanism of Drug Release from PDDS: The mechanism of drug release from PDDS can be happening in the following ways [18].

Diffusion H_2O diffuses into the internal of the particle when particles are available in contact with aqueous fluids in the GIT, and consequential drug solutions diffuse across the discharge coat to the external.

Erosion A few coatings designed to erode slowly with time, bring about the discharge of drug contained within the particle. Osmosis An osmotic pressure may be constructed up within the internal of the particle whilst H_2O lets in coming into the external through the coating.

Classification of PDDS: Pulsatile systems are essentially time-controlled drug delivery systems in

which the system manages the lag time independent of environmental factors like enzyme, pH, GI motility, *etc*. Pulsatile drug delivery systems can be generally categorized into four classes;

1. Time-controlled pulsatile release system

- ❖ Single unit system.
- ❖ Multi-particulate system.
- ❖ Stimuli-induced pulsatile release system, Thermo-Responsive pulsatile release, chemical stimuli induced pulsatile system.
- ❖ External stimuli pulsatile release system.
- ❖ Electro responsive pulsatile release.
- ❖ Magnetically induced pulsatile release.
- ❖ Pulsatile release systems for vaccine and hormone products.

Time-controlled Pulsatile Release System: These time-controlled systems can be classified as a single units (*e.g.*, tablet or capsule) or multiple unit systems.

1. Single Unit Systems:

A) Capsular Systems: Single-unit systems are mostly urbanized in capsule form. The insulate time is managed by a plug, pushed away by erosion or swelling, and the drug is launched as a Pulse from the insoluble pill frame. For *e.g.*, Pulsincap gadget is one such system that comprises a water-insoluble tablet enclosing the drug reservoir. A swellable hydrogel plug was used to seal the drug substances into the tablet body [19]. When this tablet got here in contact with the GI fluid or dissolution fluid, it swelled, and after a lag, the plug drove itself outside the pill and rapidly released the drug. Polymers used for designing of the hydrogel plug are as follows:

- ✓ Swellable materials coated with but permeable polymer (polymethacrylates).
- ✓ Erodible compressed polymer (polyvinyl alcohol, HPMC).
- ✓ Congealed melted polymer (glyceryl monooleate).
- ✓ Enzymatically controlled erodible polymer (pectin).

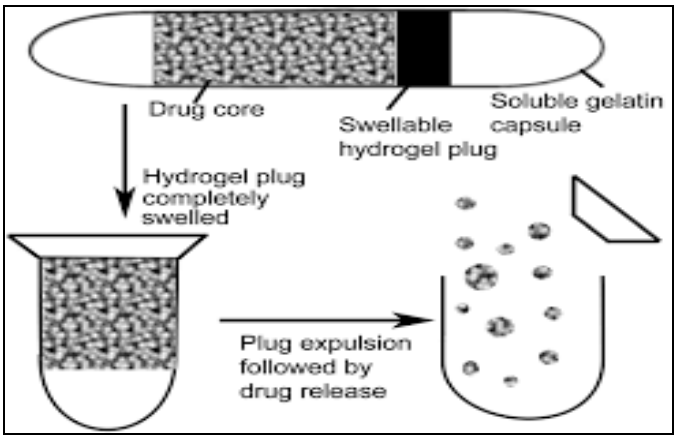

FIG. 3: SCHEMATIC DESIGN OF PULSINCAP SYSTEM. [Reproduced from: Shidhaye S.S., Lotlikar V.M., Ghule A.M., Phutane P.K., Kadam V.J. Pulsatile delivery systems: An approach for chronotherapeutic diseases. Sys. Rev. Pharm.2010; 1: 55-61.]

The duration of the plug and its point of inclusion into the tablet controlled the lag time. Pulsincap was studied in human volunteers and changed into debts to be well tolerated [20-22]. Steven *et al.* Developed a Pulsincap gadget with an erodible compressed pill [23].

As the swelling hydrogel polymer plug changed the erodible pill, the reliance of the dimensional exactness between the plug and the capsule for the pulling mechanism of the plug from the pill became an additional triumph **Fig. 3.**

Systems Based on Osmosis: The Port system consists of a capsule coated with a semipermeable membrane. The tablet became an insoluble plug consisting of an osmotically active agent and the drug method [24]. When this tablet got in touch with the dissolution fluid, the semipermeable membrane authorized the access of H_2o, which brought about the pressure to develop and the insoluble plug expelled after a insulate time **Fig. 4.**

These systems evade second-time dosing, which was helpful for school children during daytime. Another system is also based on a dispensable orifice that holds the capsular system in which liquid drug is engrossed on highly porous particles. Drug releases *via* orifice of a semipermeable capsule supported via an expending osmotic layer after the barricade layer are dissolved [25].

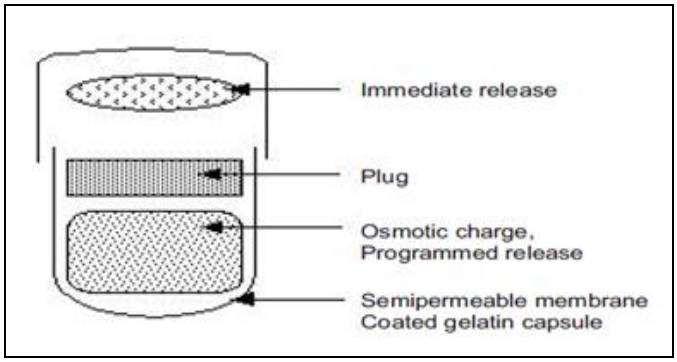

FIG. 4: SCHEMATIC DESIGN OF OSMOTIC SYSTEM. [Reproduced from:Arora S., Ali J., Ahuja A., Baboota S., Qureshi J. Pulsatile drug delivery systems: An approach for controlled drug delivery. Indian J. Pharm. Sci. 2006; 68: 295-300] Pulsatile delivery by solubilization (or) erosion of membrane

These structures are based totally on a drug reservoir bounded with a soluble or erodible barricade layer that dissolves with time, and the drug is released right now after the lag time. *e.g.* Time Clock system. It includes a strong dosage shape protected with lipid limitations consisting of beeswax and carnauba wax at the side of surfactants like PESM. When this system comes in contact with the water, the coat emulsifies or erodes after the insulate time, depending on the thickness of the coat. The insulate time of the system is unbiased of the GI motility, enzyme, pH & gastric residence [26-30]. The chronotropic gadget consists of a middle enclose drug reservoir lined with a hydrophilic polymer HPMC [31-33]. A delivered enteric-covered movie is given outdoor this layer to overcome intra-concern variability in gastric emptying costs [34]. The insulate time and movement onset are managed by the thickness and the viscosity grade of HPMC **Fig. 5.**

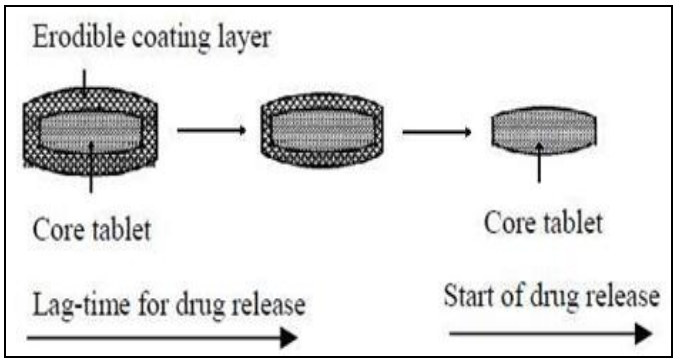

FIG. 5: SCHEMATIC DIAGRAM OF DELIVERY SYSTEM WITH ERODIBLE COATING LAYERS. [Reproduced from: Kotha R.K., Raghavapally S.G., Adavi S.L., Taranalli S., Pandey D.Current techniques in pulsatile drug delivery: a review. Int. Res. J. Pharm. 2013; 4:77-84.]

Drug Delivery System with Rupturable Layers/ Membranes: Systems are based on a reservoir coated with a ruptured membrane. The external membrane ruptures due to the pressure urbanized by effervescent agents (or) swelling agent [35-37].

Citric acid & sodium bicarbonate is included as effervescent mixture in tablet core coated with ethyl cellulose; when the system comes in contact with H_2O, it produces Co_2 gas which applies pressure & after insulate time, rupture the membrane & rapid release of the drug occurs [38].

A reservoir device with a semipermeable coating is projected, especially with pills with excessive first bypass effect to acquire *in-vivo* drug pattern much like the management of numerous instantaneous release doses croscarmellose sodium starch glycollate or low substituted hydroxy propyl cellulose was used as swelling materials, which led to entire movie rupture observed by fast drug release **Fig. 6**. The lag time is controlled by way of the composition of the outer polymeric membrane [39-42].

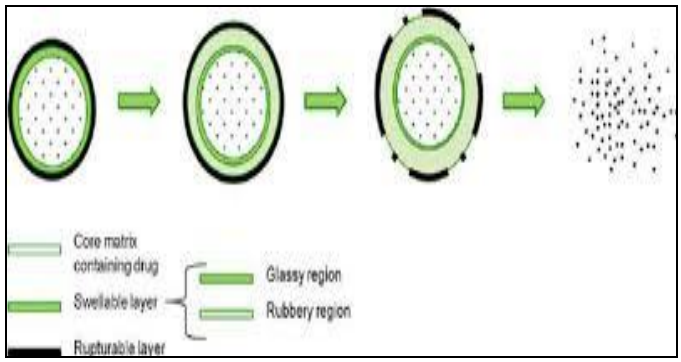

FIG. 6: DRUG RELEASE MECHANISM FROM SYSTEM WITH RUPTURABLE COATING MEMBRANE. [Reproduced from: Devi R., Kumar S. Pulsatile drug delivery system: new paradigms. Int. J. Innov. Pharm Sci. Res. 2017; 5: 34-49.]

Multiple Unit Pulsatile Systems: More dependable gastric emptying patterns are observed for multi-particulate formulations as compared to single-unit formulations, which suffer from all or none thought.

As the part of multi-particulate systems is dispersed freely throughout the GIT, their carry is affected to a lesser extent than single-unit formulations by the transit time of food [43] **Fig. 7**. These systems are of two types.

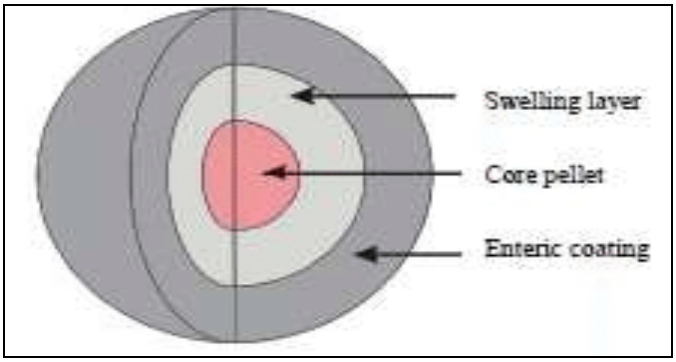

FIG. 7: HYPOTHETICAL DESIGNS OF MULTIPARTICULATE PULSATILE SYSTEMS. [Reproduced from: Kotha R.K., Raghavapally S.G., Adavi S.L., Taranalli S., Pandey D.Current techniques in pulsatile drug delivery: a review. Int. Res. J. Pharm. 2013; 4:77-84.]

Pulsatile System Based on the Change in Membrane Permeability: A-SRS is stated, primarily based upon the interface of acrylic polymers with quaternary ammonium corporations within the presence of numerous counter ions. SRS systems encompass bit cores having drug and succinic acid coated with AMC USP/NF type (B). The H_2O in the medium liquefies succinic acid. The drug within and the acid solution enlarge the permeability of the polymer film. This scheme was used to design an acid-containing core and tested in beagle dogs. It shows a good *in-vitro / in-vivo* relationship of lag time [44].

Pulsatile Systems with Rupturable Coating: Comparable to a single-unit system, the rupturing outcome is achieved by coating the individual units with effervescent (or) swelling agents. Drug transport was controlled by the break of the membrane [45-47].

The timing of discharge was controlled by the thickness of the coating and the quantity of H_2O soluble polymer to achieve the pulsed release [48]. The swelling agent includes superdisintegrants like sodium starch glycollate, carboxymethylcellulose, L-hydroxy propyl cellulose, and sodium starch glycollate. Polymers like polyethylene glycol, polyacrylic acid, *etc*. are a mixture of tartaric acid & sodium bicarbonate that are used as effervescent agent [46].

Stimuli-induced Pulsatile Release System: Stimuli-based drug delivery systems discharge the drug in rejoinder to stimuli precipitated by the organic surroundings. Discharge of the drug in rejoinder to those systems results from stimuli-induced modifies in the micelles or in the gels, which may deswell, erode or swell in response to the particular stimuli. The drug is released after inspiration by any biological factor, like temperature or other chemical stimuli [49-50]. These schemes are considered brilliant delivery candidates since they can be modified according to the job to be achieved.

Thermoresponsive Pulsatile Release: Hydrogels that endure reversible volume changes in rejoinder to changes in temperature are known as thermos-sensitive gels. Thermo-sensitive hydrogels have been inspected as possible drug delivery carriers for stimuli-reactive drug delivery. Hydrogels are cross-linked systems of synthetic, semi-synthetic, and biological polymers. These gels contract at a transition temperature that is linked to the decreased crucial solution temperature of the linear polymer from which the gel is completed. Temperature-sensitive polymer systems are characterized by hydrophobic groups, such as ethyl, methyl, and propyl groups. Poly (N-isopropyl acrylamide) (PINPAm) is possibly the most extensively used temperature-sensitive polymers. PINPA crosslinked gels have shown thermo responsive, irregular swelling/ deswelling phases. *Krezanoski et al.* explain the use of the reversed thermal gelation system, consisting of a polyol polymer such as Pluronic [51].

Chemical Stimuli-induced Pulsatile Release: These systems discharge therapeutic agents in the presence of any biological factor like pH, enzyme, or any other chemical stimuli. One significant application of this expertise has been the progress of a system that can automatically discharge insulin in rejoinder to elevated blood glucose levels. *Kazunori et al.* [52] urbanized a gel unruffled of PNIPAAm with phenylboronic acid moieties that showed an extraordinary change in the swelling induced by glucose. This type of glyco-sensitive gel may be useful in self-regulated drug releasing systems and other applications, such as regulators, actuators, and separation systems with glycol sensitivity. pH-dependent structures for glucose-stimulated drug delivery are based totally on the oxidation reaction of glucose to gluconic acid, catalyzed by glucose oxidase, which could lower pH to about 5.8 in glucose-wealthy surroundings, together with the bloodstream after a meal. This

reaction may be used to pressure the swelling of a pH-dependent covering. A dual membrane system was shaped, with the 1st membrane called the glucose-sensing membrane, wherein glucose oxidase became immobilized on cross-connected polyacrylamide. The 2nd membrane worked as a boundary between the insulin reservoir and the sensing membrane calm of N, N-diethyl aminoethyl methacrylate, and 2-hydroxypropyl methacrylate; it shaped the barricade membrane [53-54].

Externally Regulated Pulsatile Release System:

Electro Responsive Pulsatile Release: An electric field as an exterior stimulus has compensation, such as accessibility of equipment that allows accurate control with the observation of the magnitude of the current, duration of electric pulses, the interval among pulses, *etc*. Electrically responsive delivery systems are prepared from polyelectrolytes (polymers that contain a comparatively excessive concentration of ionizable corporations alongside the spine chain) and are pH and electro-responsive. Under the sway of the electric area, electro-responsive hydrogels generally erodeor swell. Poly (2-acrylamide-2-methyl propane sulfonic acid-co butyl methacrylate) hydrogels were used for electric stimuli-induced drug delivery systems [55-56].

Micro Electro-mechanical Systems: A micro made-up device can store and discharge multiple chemical substances on requiring by a mechanism devoid of moving its parts. The digital ability of MEMS may permit better temporal control over drug discharge compared to traditional polymer-based systems. Another development in MEMS technology is the microchip. It consists of a display of reservoirs that expand through an electrolyte-impermeable substrate. The prototype microchip is silicon and contains a number of drug reservoirs; each reservoir is conserved at one end by a thin gold casing of material that provides an anode in an electrochemical reaction and melts when an electric potential is applied to it in an electrolyte solution. The reservoirs are filled with any grouping of drug or drug mixtures in any form (i.e., liquid or gel, solid). When a release is favored, an electric potential is applied among an anode membrane and a cathode. The gold membrane anode dissolves within 10-20 seconds and permits the drug in the reservoir to be released. This electric potential reasons oxidation of the anode material to form a soluble complex with the electrolytes, which then dissolves, allowing drug discharge. Multifaceted release patterns can be achieved from the microchips and have the facility to control both release rate and release time [57-58].

Magnetically Induced Pulsatile Release: Utilizing an oscillating magnetic to adjust the drug delivery from a polymer matrix was one of the first methodologies to inspect to develop an externally controlled drug delivery system. Magnetic carriers collect a response to a magnetic field from included materials, such as nickel, cobalt, magnetite, iron, *etc*. For biomedical applications, magnetic carriers must be non-toxic, biocompatible, water-based and non-immunogenic. Essentially the mechanistic approach behind the approach is based on slowing down the movement of oral drugs in the GI system through magnetic magnetism. This is possible by satisfying an additional magnetic component into capsules or tablets **Fig. 8**. The speed of journey through the stomach and intestines can then be slowed down at exact positions by an external magnet, thus changing the timing and/ or amount of drug absorption into the stomach or intestines [59-63].

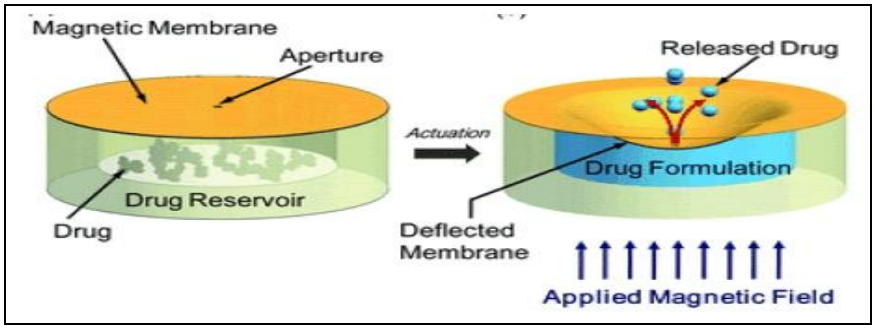

FIG. 8: DRUG RELEASE FROM MAGNETICALLY INDUCED PULSATILE SYSTEMS. [Reproduced from:Shanmugan P., Bandameedi R. Chronotherapeutic drug delivery systems. J. Drug Meta. Toxico. 2015; 6: 2-7.]

Pulsatile Release Systems for Vaccine and Hormone Products: Vaccines are conventionally administered as an original shot of an antigen followed by frequent booster shots to produce defensive immunity [64].

The incidence of the booster shots and hence the precise immunization- schedule is antigen reliant. Also, co-administration of vaccine adjuvant is often required to enhance the immune response to achieve defensive immunity [65]. PDDS offers the possibility of single-shot vaccines if early booster discharge of the antigen can be achieved from one system in which the timing of booster discharge is controlled.

Marketed Technologies of Pulsatile Drug Delivery: A lot of work is being done to attain pulsatile release so that the drug discharge can be delivered according to our body's circadian rhythms. Currently, pharmaceutical companies have been paying attention to rising and commercializing PDDS that complete unmet medical needs in treating various diseases. Recently urbanized technologies are listed in **Table 1.**

TABLE 1: EXAMPLE OF FDA-APPROVED PULSATILE DRUG DELIVERY SYSTEMS IN MARKET

Proprietary name	Active pharmaceutical ingredient	Chronopharmaceutical technology	Drug release mechanism
Concerta® tablet	Methylphenidate HCl	OROS	Osmotic regulation
Cardizem LA	Diltiazem Hcl	CEFORM microsphere technology	Diffusion/ erosion
Uniphyll^{R}	Theophylline	CONTIN^{R}	Controlled release
Innopran^{R} XL	Propranolol Hcl& Verapamil	DIFFUCAPS	Rapid/sustained release
Covera-HS^{R}	Verapamil	OROS	Osmotic regulation
Verelan^{R} PM	Verapamil	CODAS	Delayed release
Pepcid	Famotidine	Physicochemical modification of API	Tablet
Lipovas^{R},	Simvastatin	Physicochemical modification of API	Tablet
Invega^{TM}	Paliperidone	OROS	Osmotic regulation
Glucotrol	Glipizide	OROS	Osmotic regulation
Glizid-MR30	Gliclizide	Hydrophilic matrix technology	Swelling/diffusion/erosion
KAPIDEX^{TM}	Dexlansoprazole	DDR Technology	Dual drug release
Coruno®	Molsidomine	Geomatrix technology	Swelling/erosion
Theirform	Diclofenac sodium	3DP	Immediate release/controlled release
PulsincapTM	Dofetilide	PulsincapTM	Rupturable system
MOXATAG®: ER tablets	Amoxicillin	PULSYSTM	Multiparticulate system
Their form	Diclofenac Na	Three dimensional printing	Externally regulated system
OPANA®	Oxymorphone	TIMERx®	Erodible/ soluble barrier coating ER Tablets
Cardiazem® LA	Diltiazem HCl, Verapamil HCl	CEFORM®	Extended Release tablet
Procardia XL	Nifedipine	PROCARDIA XL®	Sustained release
Hokunalin® tape	Tulobuterol	Transdermal chronodelivery System.	

Diseases Requiring Pulsatile Drug Delivery: Thorough knowledge of the disease body structure is needed earlier than designing the pulsatile drug delivery system. In a disorder in which rhythmic circadian employer of the frame performs a vital role, the medicine's pharmacokinetics and/or pharmacodynamics are not regular within 24 h. **Table 2** Enumerates diverse diseases showing this type of chronological behavior [66-69].

TABLE 2: TARGETS FOR PULSATILE DRUG DELIVERY

Diseases	Chronological behaviour	Drugs used
Asthma	Precipitation of attacks during night or at early morning	Antihistamines, B2 agonist
Attention deficit syndrome	Increase in DOPA level in afternoon	Methylphenidate
Arthritis	Pain increase in early morning caused by the marked release of inflammatory cytokines, including interleukin-	NSAIDs, Glucocorticoids

	6 in the early hours of the morning	
Cancer	Blood flow to tumour is threefold greater during each daily activity phase of the circadian cycle than during the daily rest phase	Vinca Alkaloids, Taxans
Duodenal ulcers	Gastric acid secretion is highest at night bowel motility and gastric empting are slower at night	Proton pump inhibitors
Peptic ulcers	Acid secretion is high in afternoon & at night	H2 blockers
Hypercholesterolemia	Cholesterol synthesis is generally higher during the night than day time	HMG CoA reductase inhibitor
Diabetes mellitus	Increase in blood sugar level after meal	Sulfonylurea, Insulin
Cardiovascular disease	BP is at lowest during the sleep cycle	Nitro-glycerine, CCBs, ACE inhibitors
Neurological disorder	Central pathophysiology of epilepsy and behavioural classification of convulsive events	MAO-B inhibitor
Allergic rhinitis	Worse in the morning/upon rising	Antihistaminics
Hormone secretion	Growth hormone and melatonin are produced at night testosterone and cortisol in morning hr	Corticosteroids
Angina Pectoris	Chest pain and ECG changes more common in the early morning	Antianginal drugs
Myocardial Infraction	Incidence higher in the early morning	Cardiovascular agents
Stroke	Incidence higher in the morning	Cardiovascular agents
Sudden cardiac death	Incidence higher in the morning after awakening	Cardiovascular agents

Recent Advances in the Pulsatile Drug Delivery System: Pulsatile drug delivery systems have huge significance in various disease conditions, especially in diabetes, where the dose is optional at different intervals. The multi-particulate systems (*e.g.,* pellets) offer a range of advantages over a single unit.

The release pattern of pellets can be of any type like pH-dependent, time-dependent, or microflora-activated system. Huge interest is taken in time and site-specific oral drug delivery to improve therapeutic efficacy. GRDD system is a proposal to prolong gastric residence time, thereby targeting site-specific drug release in the upper GI tract. FDDS and bio-adhesive drug delivery are broadly used techniques for gastro retention. Various pulsatile technologies have been developed based on methodologies as discussed formerly [69-71].

ACCU-Break Technology: This skill is designed to easily isolatable tablets in exact smaller doses, thus, dosage modification becomes easy. In ACCU-T-CR Trilayer tablets contains a controlled-release medication or immediate release component. It gets separated by a drug-free rupture layer which allows the CR dose to be divided into precise half doses.

TMDS Technology: The Time Multiple Action Delivery System provides organize release rate of multiple ingredients within a single tablet.

Geo-clock Technology: Chronotherapy alert press coated tablets are used in which an active drug remains surrounded by an outer tablet layer consisting of a mixture of hydrophobic wax and brittle material. In this way, a pH-independent lag time is obtained. *E.g.,* LODOTRA – for rheumatoid arthritis.

DUREDAS Technology (Dual Release Drug Absorption System): A bilayer tablet was manufactured in which one layer provided immediate release action and the second layer provided sustained release action.

KV/24: One or additional drug compounds remain encapsulated to articulate the release of the drug in a predetermined fashion. Prior to coating with one or more polymers, a neutral core is coated with a drug substance to attain a once-a-day release profile. The drug can be combined in two ways, one with the neutral core second included in the coating process.

INNOHERB: Pellets are coated within the capsule. Preferred active herbal compound rehabilitated into micro pellets or small beads. A semipermeable membrane carries out the coating of these to advance stability and mask taste/smell.

IPDAS Technology (Intestinal Protective Drug Absorption System): The beads with high-density

drugs are dense to form controlled-release tablets. It is particularly appropriate for a tablet that causes gastro irritation and disintegrates quickly. The nature of the drug-containing bead matrix or its semipermeable membrane coating controlled the release pattern.

ORBEXA Technology: More drugs are loaded, and the product is subjected to granulation. After granulation/extrusion and spheronization, useful polymer membranes are used to coat the resulting beads for additional release rate control and may be filled into capsules. This skill can be used for responsive drugs such as proteins.

Future Possibilities and Prospects: The future of chronotherapeutics and more especially the future of delivering drugs in a pulsatile way seem to be fairly promising as in certain disease states, pulsatile release explains many advantages over the customary zero or first-order drug delivery systems. PDDS can also be time-controlled or site-specific, single or multiple units. At the moment, pulsatile release most often is achieved by using different polymers in coating layers or by altering the coating thickness. From a technological point of view, multi-particulate systems seem more competent than single-unit dosage forms in achieving pulsatile drug delivery. It can become even more sophisticated when coating technologies are included. The authors of this paper consider that an increasing number of multiparticulate coated systems would become commercially available in the years to come. **Table 3** includes the recent patent application/granted list.

TABLE 3: RECENT PATENT ON PULSATILE/CONTROLLED DRUG DELIVERY SYSTEMS/DEVICES

S. no.	Based on API/Device	Topic	Inventor	Status/Date	Patent No.
1	Device	Multi-dose drug delivery device and method	Robert Farra	Granted/ 2014-03-25	US8679093B2
2	Device	Medical device for controlled drug delivery and cardiac monitoring and/or stimulation	Barry M. Yomtov Stephen J. Herman	Granted/2011-03-29	US7917208B2
3	Device	Low-permeability, laser-activated drug delivery device	Jonathan Robert Coppeta Kenneth N. Horne John T. Santini, Jr. John A. Scholl Gregory J. R. SpoonerCynthia L. Stevenson Naveed Shams Andrew Poutiatine	Grant/ 2014-12-16, 2014-01-08	US8911426B2, EP2533737B1
4	Device	Portable drug delivery device including a detachable and replaceable administration or dosing element	Joseph Zhili Huang Guy DiPierro	Grant/2013-02-12,	US8372040B2
5	Device& different APIs	Oral drug delivery system	Su Il Yum Grant Schoenhard Arthur J. Tipton John W. Gibson John C. Middleton	Grant/ 2012-03-13, 2015-09-23, 2012-02-01, 2013-06-12, 2013-09-17, 2010-11-11, 2016-01-11, 2011-01-26	US8133507B2, EP2218448B1, JP4865330B2, CN101797221B, CA2810477C, DE60334401D1, DK2218448T3, ES2350689T3
6	Delivery system	Drug delivery system	James M. Olsen	Granted/ 2010-08-03, 2007-11-14, 2008-09-11	US7766885B2, EP1755703B1, DE602005003355T2
7	Device	Cartridge insertion assembly for drug delivery system	Oz Cabiri	Granted/ 2012-04-17, 2014-08-13, 2014-07-02, 2014-05-07	US8157769B2, EP2477679B1, JP5535321B2, CN102639169B

8	Ionizable pharmaceutical agent & lipophilic species	Transmucosal drug delivery system	John A. McCarty	Granted/ 2015-03-31, 2014-04-16, 2013-01-02, 2012-02-07, 2013-07-08, 2013-07-18, 2009-01-10	US8992974B2, JP5475215B2, CN1777411B, CA2516816C, DK1599186T3, ES2414084T3, RU2342953C2
9	Devices	Drug delivery devices, kits and methods there for	Gilbert H. KLIMAN	Granted/ 2013-08-27	US8521273B2
10	Devices	Gastric retention controlled drug delivery system	Kamlesh Mohanlal Dudhara Nitin Bhalachandra Dharmadhikari Vaishali Vijay Dhavse	Granted/ 2010-08-17, 2012-12-05, 2012-08-08, 2010-12-01, 2011-06-14, 2010-09-30, 2013-03-15, 2008-05-27	US7776345B2, EP2238975B1, JP4994570B2, CN1520286B, CA2452738C, DE60237372D1, ES2398348T3, RU2325152C2
11	Device	Transmucosal drug delivery device and method including chemical permeation enhancers	Scott Uhland Eric Peeters Hussain Fatakdawala	Granted/2014-11-11, 2014-11-19, 2015-05-07	US8882748B2, EP2308465B8, JP5715368B2
12	Delivery System	Controlled dose drug delivery system	Amir Shojaei Stephanie Read Richard A. Couch Paul Hodgkins	Granted/ 2014-09-30	US8846100B2

CONCLUSION: Currently, oral drug delivery is still the preferred route due to the high patient fulfillment, ease in administration, and elasticity of its formulations. There is a steady need for new delivery systems to provide increased therapeutic profit to the patients. While sustained and controlled-release products provide a desired therapeutic impact, drop brief of diseases following organic rhythms, circadian issues, peptic ulcer, high blood pressure, osteoarthritis, and asthma which want chrono pharmacotherapy. Circadian rhythm of the body is a widespread concept for knowledge of the most reliable want of drug within the body. Pulsatile drug delivery is one such system that, through handing over drugs in the proper region, time, and amounts, holds proper assures of gain to the patients suffering from chronic problems. A sort of structures like stimuli, time, externally regulated multiparticulate regulated pulsatile thus conniving of right pulsatile drug transport will enhance the patient achievement, foremost drug delivery to the goal site and minimizes the undesired outcomes. We are sure that with an increase in technological development and higher design parameters, those obstacles can be overcome inside the close to destiny and wider variety of patients will be significantly benefited from this system.

ACKNOWLEDGEMENT: None

CONFLICT OF INTEREST: None

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How to cite this article:
Yadav R and Jain DK: Present scenario of pulsatile drug delivery system. Int J Pharm Sci & Res 2023; 14(1): 129-41. doi: 10.13040/IJPSR.0975-8232.14(1).129-41.