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A REVIEW ON PULSATILE DRUG DELIVERY SYSTEMS

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ABSTRACT: In present days, solid oral drug dosage forms are widely used and the largest part of the entire drug delivery system due to their more, easy preferable route of administration and improved patient convenience nature. Most of the oral drug delivery systems show a distinctive drug release pattern, and the drug concentration is maintained within the limit of the therapeutic range. With technological advancement, pulsatile medication delivery devices are becoming increasingly important and popular for controlled delivery systems based on drug design. It maintains the circadian rhythm of the disease conditions and reduces the side effects of the drug. So, the important action of pulsatile drug delivery systems is used to delivery the drug at right time, site or target, and quantity. The drug release follows the sigmoid al release pattern, characterized by a period of no release (lag time). These systems release or deliver the drug based on the pathophysiological need of the disease at a specific time. So, it improves the therapeutic efficacy, compliance of the patient and decreases dosing frequency.

INTRODUCTION: The Pulsatile drug delivery systems (PDDS) show great importance, interest due to complete drug release and follow the pattern of drug release after Lag time. So, the pulsatile systems are based on time, site-specific systems. Hence, these systems are designed to deliver the medication quickly and bursts in a short period after a predetermined off-release Period. So, drug release from the dosage form as a pattern of "pulse" after the lag time [1, 2].

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Two phases characterize the PDDS release: In that, the initial phase shows the release of small amount of the drug and is continued by the next phase, in which the complete release of the drug takes place in a short period of lag time [3].

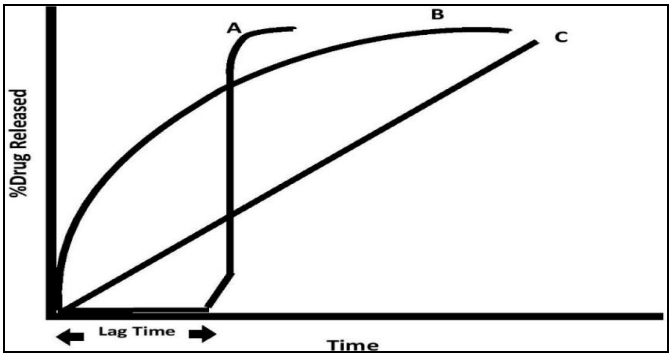

FIG. 1: RELEASE OF DRUG PROFILE FROM VARIOUS DELIVERY SYSTEMS (A) PULSATILE (B) CONVENTIONAL (C) EXTENDED

Chronobiology is the study of science concerned with biological rhythms and mechanisms. The presence of body biological rhythms is categorized into three categories as follows

TABLE 1: TYPES OF BIOLOGICAL RHYTHMS [4]

S. no.	Name of the Biological Rhythm	Oscillations Duration of time
1	Circadian (Derived from the Latin words circa means "about'' & dies means "day'').	Oscillations of a Day (Completed within a day or 24 hours)
2	Ultradian	The Oscillations are shorter durations type (>01cycle/24 hours)
3	Infradian	The Oscillations are longer durations type (<01 cycle/24 hours)

Diseases and Chrono Therapeutics [5]: Circadian rhythms are endogenous oscillations that occur periodically for about 24 hours and involve regulating many body functions of metabolism, sleep pattern, and hormone production.

TABLE 2: DISEASE, CHRONOLOGICAL BEHAVIOUR, DRUG TREATMENT [5]

Disease	Chronological Behaviour	Drugs used for treatment
Arthritis	Pain occurs at night	NSAIDS
Peptic Ulcer	Increase Acid secretion at afternoon and night sessions	H2 blocker
Asthma	During night time and early morning hours	Antihistamine, β2 blocker
Diabetes	After a meal increased level in the blood	Insulin, Sulfonylurea
Hypercholesterolemia	At night time Higher levels of cholesterol level when compared to daytime	HMG CoA reductase inhibitors
Cardiovascular disease	Reduced level of Blood pressure during sleep time and increased level in early morning	ACE inhibitors, Calcium channel blockers, Nitroglycerine
Duodenal Ulcers	Increased night-time gastric acid secretion and a slower rate of gastric emptying, gastric, small bowel motility	Inhibitors of proton pump
Cancer	Three-fold highest in the flow of blood to tumors and growth of tumors in every daily activity stage of the circadian cycle	Taxanes, Alkaloids like Vinca
Neurological disorders	The primary pathophysiology of epilepsy, classification of behavioral convulsive event	Inhibitors of MAO
Attention deficit syndrome	In the afternoon time to observe High levels of DOPA	Methylphenidate

Advantages [6, 7]:

1. It shows better and increased bioavailability and absorption processes than conventional immediate and sustained release dosage forms due to the release pattern being present in a burst manner and targeting the site.
2. Decreases the drug dose without affecting the drug's therapeutic activity.
3. Reduces the side effects compared to other conventional dosage forms.
4. It improves patient compliance nature.
5. Multiple dosing is possible in a single dose of pulse type of system.
6. Less risk of local irritation.
7. Greater stability in dosing.
8. Specific release.
9. To prevent drug loss by first-pass metabolism.
10. Suitable for the body's circadian rhythms functioning system behavior of Diseases.

Disadvantages [6, 7]:

1. Large number of manufacturing steps involved in production.
2. Production cost is also high and requires advanced technology.
3. Low drug loading capacity is possible.
4. Lack of manufacturing units.

Need of Pulsatile Drug Delivery [8]:

1. Body rhythm follows circadian rhythms.
2. Some Hormones modify the Circadian rhythm ex: rennin, aldosterone, cortisol, *etc*.
3. Some diseases like bronchial asthma, myocardial localized necrosis, angina pectoris,

rheumatic infection, ulcer, and hypertension showed time reliance.

4. Importance of Lag time is essential for some drugs that undergo degradation in gastric acidic medium conditions.

5. Some drugs undergo broad first-pass metabolism.

Mechanisms Involved in PDDS [9]: The release of drug from the dosage form follows: Diffusion type, Erosion type, and Osmosis type.

Diffusion: Release of drug from the coating material to the outside based on the diffusion process, in which water diffuses into the particle inside and shows interaction with the GI tract fluids.

Erosion- Some of the coating materials intended to dissolve steadily with time and release of the drug contained inside the molecule.

Osmosis: An osmotic agent present inside of the molecule and it interacts with the water to generate osmotic pressure so the release of drug molecules to the outside with a covering.

Methods used for PDDS:

I. Time controlled
II. Stimuli induced
III. External regulated

I. Time-controlled PDDS:

1. Single-unit pulsatile system

i) Based on Capsule type (Pulsincap System type)

ii) Based on a Capsular system with Osmosis type

a) PORT System

b) Expandable orifice System

c) Pulsatile drug delivery by solubility modulation

d) Delivery by series of stops

iii) Pulsatile system contains erodible/ soluble barrier coatings

Compressed tablets, Multilayered tablets, Time clock Systems, Chronotropic Systems.

iv) Pulsatile systems with rupturable coating

2. Multi-particulate / Multiple unit systems

i) Pulsatile system with a rupturable coating

ii) Rupturable coating by Osmotic system

iii) Pulsatile Delivery by modifications in the Membrane Permeability

II. Stimuli Induced:

i) Temperature-induced type

ii) Chemical-induced stimuli type

a) Glucose-responsive insulin release

b) Inflammation-induced

c) Release of drug from intelligent gels responding to antibody concentration

d) Electrical stimuli responsive pulsatile

e) pH-sensitive type of drug delivery

III. External Regulated:

i) Electro responsive to drug release

ii) Stimulation by ultrasonically method

iii) Stimulation by the magnetically induced method

I. Time-controlled PDDS:

Single Unit Pulsatile Systems: The single-unit systems show the release of drugs based on the capsule type of system.

Capsule-Based Type Systems-Pulsing Cap Type [10, 11]: In this type of system, the lag time is controlled by a design "Plug" and it is pushed away from the capsule by the process of swelling/erosion after that it forms a Pulse and release of the drug from the capsule body so lag time is can be modified with manipulation of dimensions, Plug position.

Polymers used for the process of designing hydrogel plug-like swellable polymers but Insoluble and permeable nature (ex: Polymethacrylates), Compressed erodible polymer nature (ex: HPMC, PVA, PEO), Congealed melted

polymer nature (ex: glyceryl monooleate), Enzymatic Erodible polymer nature (ex: Pectin).

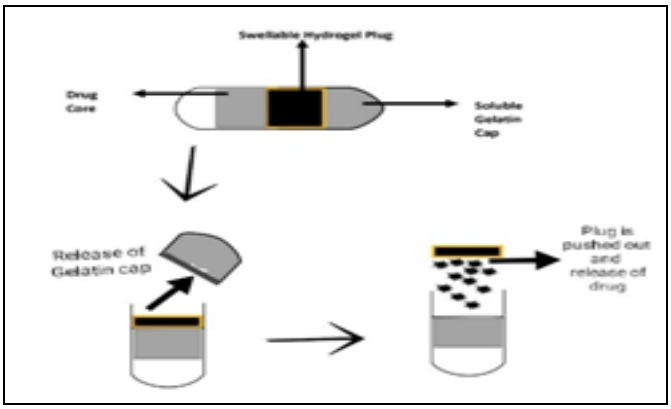

FIG. 2: PULSIN CAP SYSTEM DESIGN

Capsule Systems with Osmosis Type [12, 13]:

PORT System: It consists of a capsule with a semipermeable coating membrane. The insoluble plug is inside the capsule body and contains an insoluble plug along with an osmotically active agent and drug formulation. When the capsule's contact with the dissolution fluid, water can enter through the coated semipermeable membrane, creating pressure. The insoluble plug was expelled after the lag time and helps to avoid the second dose type.

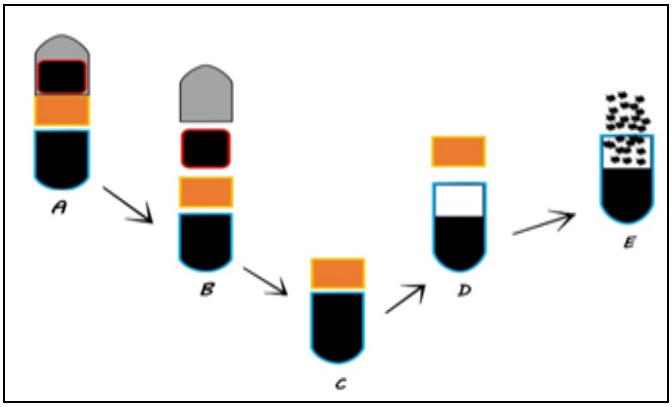

FIG. 3: PORT TYPE OF DESIGN. (A)Port type system B) Release of the drug after swelling of cap C) Permeation of GI Fluid with internal pressure generation D) Plug Release E) 2nd release of drug in sustained/Pulsed form

Expandable Orifice System [14]: In these systems, the delivery of the drug is a liquid form. So, an osmotically driven capsular system is based on the absorbed liquid drug into the highly porous particles with the help of an orifice to deliver the drug by semipermeable membrane orifice containing capsule which is enclosed by expanding osmotic layer.

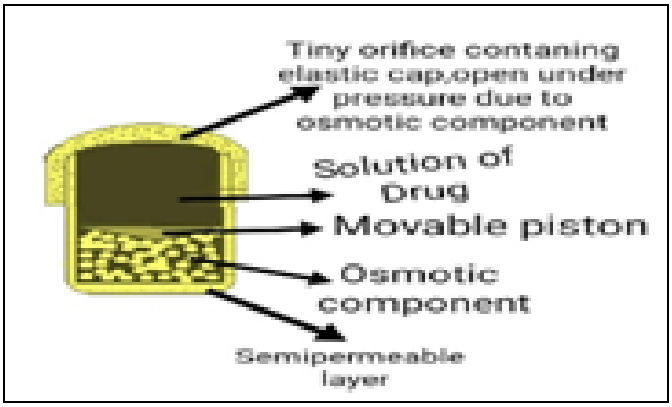

FIG. 4: EXPANDABLE ORIFICE SYSTEM

Delivery by Series of Stops [15]: It is presented for an implantable type of capsule system in which the capsule contains a drug, water absorptive osmotic agent, which is placed in the compartments with the separation of a movable partition. So, the series of stops, along with the inner wall containing the capsule which is helpful for drug delivery.

Pulsatile Delivery by Solubility Modulation [16]: It includes drug and solubility modulating agent (Sodium chloride), so delivery of drug release from the PDDS by several modifications. The pulsatile drug delivery depends on the solubility of the drug. The modulating agent used in the PDDS may be an organic acid/inorganic salt. To control the release of zero order and the beginning of the pulse release, using the ratio of the drug and modulating agent can be varied. So, after the release of the zero-order time period the drug delivers as a large pulse.

Pulsatile System Contains Erodible/Soluble Barrier Coatings [17]: It consists of a reservoir type of system with an obstruction layer. The obstruction layer erodes/break up after the particular lag period, release of drug is rapid from the reservoir core. So, the covering layer thickness influences the Lag period.

Chronotropic Systems: Drug-containing core covered by swellable hydrophilic polymers and is important for the lag time at starting drug delivery. So, the variations in the thickness and grades of polymer type influence the controlling of lag time. The changes in the film thickness achieve time clock systems-Controlling of the lag time. After that, the lag time is required for rehydration, and the drug core promptly delivers the drug.

Compressed Tablets: The process of direct compression on both core and coat material with the help of different coating methods and utilizing the coating arrangements. The outermost layer of the tablet represents the first initial dose which is fast disintegration in the stomach, and the inner layer of the tablet with a selected polymer that is insoluble nature in the gastric medium but releases the drug in the intestine.

Multilayered Tablets: Two pulses are generated with a three-layer tablet model, which consists of drug layers and is separated by a polymer of a free gellable layer.

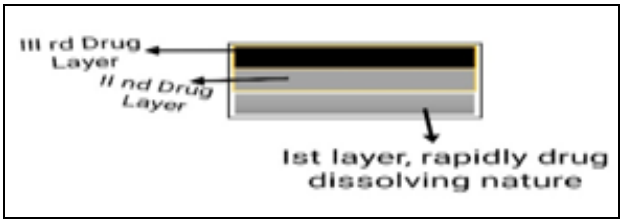

FIG. 5: MULTI-LAYERED TABLET

Multi-particulate/Multiple Unit Type Systems:

Pulsatile System with Erodible or Soluble Barrier Coatings [18, 19]: The number of PDDS systems are present in the form of reservoir type systems with a barrier layer so the used barrier is soluble, erodible in nature after a specific lag time period so the drug release rapidly from the system of drug containing reservoir core. So, the lag time period is completely depending on the coating layer thickness. In Chronotropic system drug core (In Tablets and capsules) is coated by hydrophilic swellable polymers. Conversely the lag time period is depending on the layer thickness and Viscosity of polymer grades. In compressed tablet system, the direct compression technique is used to compress coating of both the core and coat. The outer compressed coated tablet shows the initial dose with fast disintegration and the inner compressed layer consists of insoluble components in the gastric media but soluble drug, release in the intestine in multilayer tablet system.

Pulsatile Systems with Rupturable Coating [20, 21]: The release of the drug is based upon the process of coating layer disintegration. Effervescent, swelling and osmotic pressure producing excipients are used to create pressure for rupturing of the coating layer. A combination of citric acid, sodium bicarbonate is used in the core of the tablet formulation, which is completely coated with ethyl cellulose polymer so liberation of CO_2 gas after the water penetration into the tablet core results in the release of the drug as a pulsatile type after the rupturing layer of coating. Example: Time-controlled system of Explosion, in this the active medicament, is completely coated with the non-pareil sugar seeds followed by a swellable, insoluble top layer.

Rupturable Coating by Osmotic-Based Systems: It consists of a combination of both osmotic and swelling agent effects. The drug, low bulk density containing lipid substance and disintegrating agent present in the core and finally coated with cellulose acetate polymer. So, the drug core is in contact with the aq. media water penetrate into the drug core and displacing the lipid substance. The lipid material depletion leads to an increase in the internal pressure until it reaches critical stress and it shows the rupturing of the coating.

Stimuli-induced PDDS [22]: The Release of drugs by the influence of stimuli based on the factors like high temperature and any chemical agent.

Temperature-induced Pulsatile Release [23]: Thermoresponsive hydrogels are used to induce stimuli type of drug delivery. In this method, swelling and de-swelling of polymer stages occurs in response to the high temperature.

Chemical-induced Stimuli Pulsatile System:

Glucose-responsive Insulin System [24]: Several devices are designed to respond to changes in glucose concentration. The enzyme Glucose oxidase catalyzes the oxidation process of Glucose.

Inflammation-induced Pulsatile Systems [25]: In physical or chemical stress like broken bones, injury, etc., inflammation occurs at the injury site. So, at the inflammatory sites, the inflammation-responsive phagocytic sites, the macrophages, and polymorphonuclear cells play an important role in the injury process of healing.

Release of Drug from Intelligent Gels Responding to Antibody Concentration [26]: Several Bioactive components are present in the Body. Therefore, the development of novel gels with bioactive components concentration changes and alters their swelling and/or deswelling properties.

Electric stimuli responsive PDDS [27]: Iontophoresis, Infusion Pumps, and sonophoresis technologies are used to stimulate the swelling /deswelling characteristics of the polymer containing hydrogel.

pH-Sensitive Type of Drug Delivery Systems [28]: It consists of two segments. The first one is quick discharge, and the other is beat discharge type. Discharge the drug based on the response to change in pH.

External Regulated Pulsatile Drug Delivery [29]: In which the release of the drug can be externally regulated by ultrasound, electrical, magnetic, and irradiation (light) stimuli. In a magnetic regulated system, magnetic beads are placed in the implant so the drug release occurs from the magnetic field application. In an ultrasound system, the ultrasonic waves show erosion of the polymer matrix. In the Irradiation method, irradiation of light rays is used for drug release, and the light irradiation light rays desire the pattern of drug release by drug exposed to light. In Electric induced system, the presence of both electro and pH-sensitive responsive systems causes drug release.

Recent Advanced Technologies used in Pulsatile Drug Delivery Systems [30, 31]: The number of recent technologies are used for various disease treatments to release the required drug amount at different intervals. Hence, mostly multiparticulates are used compared to single unit dosage form due to greater flexibility in blending with different release patterns, dose dumping is not possible, and reproducible short gastric residence time Various PDDS technologies developed on the basis of methodologies.

TABLE 3: TECHNOLOGIES IN PULSATILE DRUG DELIVERY SYSTEMS

S. no.	Name of the Technology	Description
1	Pulsincap Technology [32,33]	The Pulsincap system consists of a non-breakable half-case body with open end type, attached with a hydrogel plug, and covered with a water-dissolving cap. So, the entire capsule is covered with an enteric polymer used to avoid gastric emptying. When the capsule interacts with the dissolution fluid medium, it shows swelling property nature after the lag time period so the attachment propels to outside and releases the drug quickly.
2	OROS [34,35] Proprietary name: Chronset	The delivery system delivers the drug reproducibly based on the time or site-specific model in the GIT. It is completely based on the Osmosis model, in which the tablet containing the drug is present in the form of a reservoir enclosed by the semipermeable membrane with a laser-drilled orifice to deliver the drug. The bilayer and trilayer tablet systems consist of two layers with drug and osmotically active agents. When contact with the GI fluid the osmotically active agent generates the pressure and pushes the drug layer and releases of a drug through an orifice.
3	IPDAS[36]	It is another type of oral approach system of medication used for GI aggravation medications like NSAID category. So, this type of innovation is completely based on multiparticulate systems, in which high thickness/density-controlled discharge dots/beads are compacted into the tablet form. After ingestion of the IPDAS tablet, the rapid disintegration of the tablet, scatter globules containing the drug in the stomach, passes through the duodenum along with the GI tract in a continuous and controlled release manner. The drug release is based on the process of diffusion through a layer of polymer or micro matrix system of drug-polymer formation in the extruded multiparticulate system.
3	CEFORM [37,38]	It consists of a uniform size and shape containing spherical microspheres with 150-180mm with high drug based on the process of melt spinning method in which the biodegradable polymer with combination to temperature, mechanical type of force, thermal gradients and flow of rate during the process. So, the obtained microspheres are used in a number of dosage forms like Capsules, tablets, suspensions, and effervescent-type tablets. The coated microspheres with enteric polymers are used for controlled release.
4	DIFFUCAPS [37-39]	The capsule-based system with single or more drug particles includes beads, pellets and granules. Each particle expresses the preprogrammed release pattern with rapid /sustained action with /without a lag time. Diffucap system comprises a number of layers with drug release-controlling polymers and Excipients. The particles contain the organic acid/alkaline buffer, which is used to control the drug solubility.
5	EGALET [39,47]	Delayed release type of system with an impermeable shell containing two lag plugs enclosing the drug plug present in the middle of the unit. So, by erosion, an inert plug leads to drug release. The time taken to erode the inert plug determines the lag time. The shells are made up of plasticizers and biodegradable polymers but the mixture of plugs are pharmaceutical additives

		that are polymer like polyethylene oxide.
6	CHRONOTOPIC [40]	It is similar to a soluble erodible/rupturable membrane type of system. It comprises of drug core and is coated with an outer controlling release layer. The unit type of single, multiple dosage forms like tablets, capsules, mini type of tablets, pellets are used as inner formulations of the drug in the dosage form.
7	CODAS [41]	It is a multiparticulate system for bedtime dosing. In which non-enteric coating layers are applied to drug beads, to delay the drug release up to 04-05hrs. For coating, the polymers of water-soluble and insoluble are used so the dosage form interacts with the GI fluid, the water-soluble polymer slowly dissolved to create apertures or pores on the coated layer; thereby the drug diffuses from the pores, and water-insoluble polymer represents the barrier and to maintain the drug release in a controlled manner.
8	TIMERx [42]	This system is a hydrogel-based type device with controlled release. It provides the release of drugs from zero to chronotropic and shows different release kinetics. Basically, this system contains xanthan gum and locust bean gum by dextrose so a physical interaction occurs between the compounds to form a strong gel bonding in the presence of water. The release of the drug is controlled by the penetration of water, from the GI fluid into the TIMERx type of gum matrix system and expansion occurs finally to form a gel, release of the drug.
9	SODAS [42,43]	It is a high-density type of multi-particulate system proposed for GIT irritant compounds and the controlled release beads characterized by its inherent flexibility nature. Consequently, it includes immediate drug release followed by sustained drug release and it is maintained for up to 24hrs.
10	PULSYS [42-44,47]	This type of technology is used in the Chrono therapeutic system of amoxicillin. The importance of this system used by antibiotics shows a very effective nature against fast-growing bacteria. In the Immediate type of release system administration, the response of bacteria is a dormant stage, but in the pulsatile system, it is very effective due to the release of drug pulses after regular intervals of time and doesn't allow the bacteria again into the dormant stage.
11	GEOCLOCK [45]	In this type, the tablet layers contain the drug inside and a combination of hydrophobic wax and brittle components outside to get the pH-independent lag prior to the drug core delivering the drug at a programmed drug release rate. Thus, this dry type of coating method was developed to design the slow and fast release of the drug by first releasing the inside layer of the tablet after the surrounding outer layer shell disintegrates gradually.
12	DIFFUTAB [46]	The Diffutab technology contains a fusing mixture of waxes and polymers (hydrophilic nature) which controls the discharging of drugs through the dissemination, and disintegration of grid tablets. This system is valuable in high-portion drugs with supporting drug delivery, once-a-day dosing.
13	MINITABS [47]	The small size(mm) tube shaped (2×2) tablets covered with a layer of film to control the drug's discharge rate. So, the minitabs contain a gel nature containing components that are used to control the discharge rate of the drug but in some cases additions of extra layers are used to control the delivery of the drug.
14	3D PRINTING [47,48]	This technique is helpful in the complications of internal geometries, different densities and chemicals. By using this technique, A number of oral drug delivery complex devices are fabricated into immediate, extended-release, pulse release and Dual pulse tablets. So, in this product formation the design by a computer screen as 3D type of model but before their actual implementation of the preparation process.
15	ORBEXA [49]	The innovation is a multiparticulate type of system that permits high content of drug loading and depends on the granulation process. Using the techniques of granulation, spheronization and expulsion produces the controlled size, thickness of dots and is used in different types of drug delivery like postponed discharge, site-specific, supported and pulsatile delivery. The obrexa dots are filled in the single portion of sachets/Cases.

TABLE 4: LIST OF MARKETED PULSATILE DRUG DELIVERY TECHNOLOGIES [50-54]

S. no.	Name of the Drug in the Market product	Registered trade mark	Technology used	Indication
1	Verapamil HCl	Coveras-HS	OROS	Hypertension
2	Paliperidone	Invega	OROS	Schizophrenia
3	Diltiazem HCl	Cardizem LA	CEFORM Technology	Hypertension
4	Oxybutynin HCl	Cystrin Cr	TIMERx	Urinary incontinence
5	Verapamil HCl	Innopran XL	DIFFUCAPS	Hypertension
6	Oxymorphone	OPANA	TIMERx	Pain management
7	Verapamil HCl	Verelan PM	CODAS	Hypertension
8	Famotidine	Pepcid	Drug modifications in	Ulcer

			Physicochemical properties	
9	Theophylline	Uniphyl	Contin	Asthma
10	Simvastatin	Zocor	Drug physiochemical modification	Hypercholesterolemia
11	Methylphenidate HCl	Ritalin LA	SODAS	Attention deficit hyperactivity disorder
12	Molsidomine	Coruno	Geomatrix	Chronic angina pectoris

CONCLUSION: In oral-type of dosage forms, the Sustained, controlled drug delivery systems showed great success in the delivery of medication but failure in the drug delivery given to the circadian behavior of the diseases. Hence, the pulsatile systems are very beneficial and increase the therapeutic effectiveness of the medication and improve the patient compliance effect in chronic problems. The pulsatile drug delivery systems deliver the drug at the right time, place, and amount. So, these systems are very beneficial to the patients based on the circadian behavior of the disease**.** The circadian time structure, disease rhythm pathophysiology, and medicine Chrono pharmacology knowledge help develop and design chronotherapeutic dosage forms and effective treatment of disease with minimizing the undesirable effects, target drug delivery, and non-constant dosing.

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REFERENCES:

1. Sharma Ritikha, Singh Arjun, Kumar Sunil and Jamil Faraz: Pulsatile drug delivery system. International Journal of Pharmacy 2012; 3(7): 103-107.
2. Albadri AA, Abdulbaqi MR and Almajidi YQ: Recent Trends in Chronopharmaceutics, Pulsatile Drug Delivery System. Al Mustansiriyah Journal of Pharmaceutical Sciences 2019; 19(4): 41- 49.
3. Sanjay S. Jain, Hemanshu V. Agarwal, Pramod S. Jagtap, Neha M. Dand, Kisan R. Jadhav and Vilasrao J. Kadam: Pulsatile drug delivery system (PDDS): A Brief Overview. Research J of Pharmacy and Techn 2012; 5(4): 449-461.
4. Zhao M, Xing H, Chen M, Dong D and Wu B: Circadian clock-controlled drug metabolism and transport. Xenobiotica 2020; 50(5): 495-05.
5. Patwekar SL and Barmade MK: Controlled release approach to Novel Multiparticulate Drug Delivery System. International Journal of Pharm Sciences 2012; 4: 756-63.
6. Ravichandiran V, Suba V, Senthil Nathan B, Raja Chandrika K, Padma Priya S and Saraswathi T: Pulsatile Drug Delivery Systems. Biomedical and Pharmacology Journal 2009; 2(2): 227-234.
7. Amit A Dhengale, A. Darekar and R. Saudagar: A Review-Pulsatile Drug Delivery System. Research Journal of Pharmaceutical Dosage Forms and Technology 2016; 8(3): 221-227.
8. Rompicharla B, Prabha KS and Tabasum M: A Comprehensive mass review of Pulsatile Drug Delivery System. Inter Research J of Pharmacy 2012; 3(3): 106-08.
9. Mayur D. Doshi, Niranjan D. Chivate, Anuradha N. Chivate and Tejaswini Shingate: A Systemic Review on Pulsatile Drug Delivery System with Colon Specificity. Research J of Pharmacy and Tech 2013; 6(12); 1459-67.
10. Rama B, Sandhiya V, Swetha M, Rathnam G and Ubaidulla U: Pulsatile drug delivery: a comprehensive review. International Journal of Pharmaceutical Development & Technology 2016; 5: 125-30.
11. Rada SK and Kandukuri S: Chronotherapeutic systems: Novel systems of drug delivery. International Journal of Pharmaceutical Sciences & Research 2022; 13(1): 86-94.
12. Kulakarni RV and Biswanath SA: Electroresponsive polyacrylamide grafted xanthan hydrogels for drug delivery. Journal of Bioactive and Compatible Polymers 2009; 21: 4045-4049.
13. Sirisha VNL, Namrata M, Sruthi B, Harika I, Kiran Kumar P, Kiran Kumar Rao Y and Pranavi K: Pulsatile Drug Delivery System-A Review. Inter J of Pharmaceutical Research & Allied Sciences 2012; 1(3): 13-23.
14. Gajbhiye M, Kadam V, Jadhav K and Patel J: Pulsatile drug delivery system. J of Pharma Res 2010; 3(1): 120-12.
15. Balaban SM, Pike JB, Smith JP and Baile CA: Osmotically driven delivery devices with pulsatile effect. US Patent 5209746; 1993.
16. Magruder PR, Barclay B, Wong PSL and Theeuwes F: Composition comprising a therapeutic agent and a modulating agent. US Patent No.4851229; 1989.
17. Nief RA, Sulaiman HT and Jabir SA: Pulsatile drug delivery system - A review article. Journal of Pharmacy Research 2018; 12(5): 764-70
18. Sangali ME, Maroni A, Zema L, Busetti C, Giordano F and Gazzangia A: *In-vitro* and *in-vivo* evalution of an oral system for time and/or site-specific drug delivery. Journal of Controlled Release 2001; 73(1): 103-110.
19. Rupali V. Khankari and Sneha M. Umale: A Review on Pulsatile Drug Delivery System. Asian Journal of Pharmacy and Technology 2020; 10(2): 121-124.
20. Dey NS, Majumdar S and Rao MEB: Multiparticulate drug delivery systems for controlled release. Tropical Journal of Pharmaceutical Research 2008; 7(3): 1067-1075.
21. Ueda S, Ibuki R, Kimura S, Takahasi T, Tokunaga Y and Hata T: Development of a novel drug release system, time-controlled explosion system relation between lag time and membrane thickness. Chemical and Pharmaceutical Bulletin 1994; 42(2): 364-367.
22. Youan BC: Chronopharmaceutics: gimmick or clinically relevant approach to drug delivery. Journal of Controlled Release 2004; 98(3): 337-353.
23. Anilkumar SN, Kavitha K and Vinaykumar K: Development of Chronopharmaceutical drug delivery

system of Trimetazidine HCl for Angina Pectoris. Inter J of Drug Development & Research 2010; 2(2): 371-378.
24. Sandeep Singh and Marinakoland: Formulation and Evaluation of pulsatile drug delivery systems of glipizide for the management of Type-II Diabetis mellitus. Journal of Drug Delivery & Therapeutics 2016; 6(1): 11-18.
25. Gandhi BR, Mundada AS and Gandhi PP: Chronopharmaceutics: As a Clinically relevant drug delivery systems. Drug Delivery 2011; 18(1): 1-18.
26. Janugade BU, Patil SV and Lade PD: Formulation and Evaluation of press coated montelukast sodium tablets for pulsatile drug delivery system. International Journal Chem Tech Research 2009; 1(3): 690-691.
27. Mastiholimath VS, Dandagi PM, Jain SS, Gadad AP and Kulakarni AR: Time and pH dependent colon specific pulsatile drug delivery of Theophylline for nocturnal asthma. Inter J of Pharmaceutics 2006; 328: 49-56.
28. Qureshi J, Mohd A, Ahuja A, Baboota S and Ali J: Chronomodulated drug delivery system of Salbutamol sulphate for treatment of nocturnal asthma. Indian Journal of Pharmaceutical Sciences 2008; 70(3): 351-356.
29. Cutolo M and Straub RH: Circadian rhythms in Arthritis-Hormonal effects on the immune/inflammatory reaction. Autoimmunity Reviews 2008; 7: 223-228.
30. Rewar S, Bansal BK, Singh CJ and Sharma AK: Pulsatile drug delivery release technologies-An overview. International Journal of Research and Development in Pharmacy and Life Sciences 2015; 4(2): 1386-93.
31. Amritha R, Sivakumar R and Haribabu Y: A Review on Pulsatile Drug delivery system-Drug scheduling based on biological rhythm. Research Journal of Pharmacy and Technology 2022; 15(3): 1359-4.
32. Hema J, Vaseem AA, Pandit JN and Farogh A: Pulsatile drug delivery system: An overview with special emphasis on Losartan and Captopril. Research Journal of Pharmacy and Technology 2019; 12(7): 3175-3188.
33. Jose S, Dhanya K, Cinu TA, Litty J and Chacko AJ: Colon targeted drug delivery-Different Approaches. Journal of Young Pharmacists 2009; 1(1): 13-19.
34. Mathew, Sibi S, Mathan, S, Sreekumar, Meenu, Dharan and Shaiju S: Recent Technologies in Pulsatile Drug Delivery: A Review. Journal of Pharmaceutical Sciences and Research 2020; 12(10): 1336-40.
35. Anchal Sharma, Bhupendra Singh and Amit Choudhary: Quality by Design approach for the formulation of dual release drug delivery system: A Chronomodulated approach. International Journal of Pharmaceutical Sciences and Research 2021; 12(6): 3058-3068.
36. Kaur K, Seth N and Gill NS: Advancement in chronotherapeutic drug delivery system: marketed technologies and current scenario. J of Pharmaceutical Sciences and Research 2019; 11(5); 1984-9.
37. Singh A, Dubey H, Shukla I and Singh D: Pulsatile drug delivery system-An approach of medication according to Circadian rhythm. Journal of Applied Pharmaceutical sSciences 2012; 2(3): 166-176.
38. Moturi Vihar Khan and Arshad Bashir: Chronotherapeutic in development of pulsatile delivery systems. International Journal of Pharmaceutical Sciences and Research 2012; 3(11): 4086-4095.
39. Kumar RS and Mangesh Pradeep Kulkarni: Indo American J of Pharmaceutical Research 2018; 8(1): 1189-1197.
40. Dashevsky A and Mohamad A: Development of pulsatile multiparticulate drug delivery system with aqueous dispersion Aquacoat ECD. International Journal of Pharmaceutics 2006; 318: 124-131.
41. Shah Radhika, Doshi Nidhi, Patel MR and Patel KR: Pulsatile drug delivery-A Review. International Pharaceutica Sciencia 2012; 2(2): 45-52.
42. Roaa A. Nief, Halah Talal Sulaiman and Saba Abdulhadi Jabir: Pulsatile drug delivery system- A Review article. Journal of Pharmacy Research 2018; 12(5): 764-770.
43. Shidhaye S, Dhone A, Budhakar T and Surve C: Technologies in pulsatile drug delivery systems. International Journal of Advances in Pharmacy Biology and Chemistry 2012; 1(4): 438-445.
44. Saigal N, Baboota S, Ahuja A and Ali J: Multiple -pulse drug delivery systems-Setting a new paradigm for infectious disease therapy. Expert Opinion on Drug Delivery 2009; 6(4): 441-452.
45. Patel Vipul P and Sonjwala Moinuddin M: Pulsatile drug delivery systems for treatment of various inflammatory disorders-A Review. International Journal of Drug Development & Research 2012; 4(3): 67-87.
46. Jain D, Raturi R, Janin V, Bansal P and Singh R: Recent technologies in pulsatile drug delivery systems. Biomatter 2011; 1: 57-65.
47. Dubey and Harikesh: Pulsatile drug delivery system: an approach of medication according to circadian rhythm. J of Applied Pharmaceutical Science 2018; 2(3): 166-76.
48. Yu DG, Zhu Lm, Branford-white CJ and Yang XL: Three-dimensional printing in Pharmaceutics-Promises and Problems. J of Pharm Sciences 2008; 97: 3666-3690.
49. Kalantzi LE, Karavas E, Koutris EX and Bikiaris DN: Recent advances in oral pulsatile drug delivery. Recent Patents on Drug Delivery & Formulations 2009; 3: 49-63.
50. Pani L and Marchese G: Excepted clinical benefits of paliperidone extended-release formulation when compared to risperidone immediate release. Expert Opinion on Drug Delivery 2009; 6(3): 319-331.
51. Modi MP, Prasanth VV and Mathew ST: Pulsatile-A tool for circadian rhythm-A Review. Journal of Drug Delivery and Therapeutics 2012; 2: 58-65.
52. Kamalpuria N, Dhir S and Jain S: The latest methods and technologies of pulsatile drug delivery system-A Review. International J of Pharm Life Sciences 2017; 8: 46-58.
53. Vidhi R. Patel and Vipulbhai P. Patel: Pulsatile drug delivery systems-A Review. International J of Pharma Sciences and Research 2015; 6(9): 3676-3688.
54. Syed Gouse Firoz, Kothai R and Arul B: Novel approaches for pulsatile drug delivery systems. J of Critical Reviews 2020; 7(13): 2282-2289.

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