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AN UNDERSTANDING OF PULSATING DRUG DELIVERY SYSTEM – A REVOLUTIONARY APPROACH IN PHARMACEUTICAL SCIENCE

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ABSTRACT: Pulsatile drug delivery systems (PDDS) have attracted attraction because of their multiple release system. Pulsatile drug delivery systems are the new approach to overcome patient non-compliance over commercially used dosage forms. These techniques also help in treating the disorders based on circadian paradigm and the drugs are rapidly released according to the lag time decided by the carrier medium. This review covers different techniques of pulsatile drug delivery system and their marketed products. Biological rhythms play a pivot role in tolerance of any medicine given for the treatment of any disorder. This system enables the active drug for target action and inflated bioavailability with increased pharmacokinetics as well as pharmacodynamics profile of active moiety. The present review state diseases wherein pulsatile drug delivery systems are promising include asthma, peptic ulcers, cardiovascular ailments, arthritis and attention deficit syndrome in children and hypercholesterolemia. The author attracts attention of pulsatile drug delivery technique in Medical and for establishment in Pharmaceutical field simultaneously.

INTRODUCTION: In the era of modernization, Pulsatile drug delivery is the upcoming technique to provide patient compliance, of deliver right amount of drug to the target organ at proper time, that's why it is also called Time released drug delivery system. Pulsatile drug delivery system release their active moiety within a short time period of time to produce its therapeutic action immediately after predetermined off release period. The main objective of this system is to incorporate pulsatile effect in the system to release active drug as "pulse" after a lag time in such a manner that rapid drug release pattern should follow the lag time.

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In the recent studies, the use of pulsatile system is observed in xenobiotic having chronopharmacological behaviour (circadian rhythm) [1].

Chronopharmaceutics:

Chronopharmaceutics may be considered as a connection to fill the gap in between chrono biology, chrono pharmacology, chornopharma cokinetics, chronotherapeutics and chronotoxicology. Chronotherapeutics takes into account predictable administration time-dependent variation in the pharmacokinetics of drugs as well as the susceptibility of target tissues due to temporal organization of physiochemical processes and functions of the body as circadian and other rhythms. Chronotherapeutics approach to increase the efficiency of pharmacotherapy is the administration of drugs at times at which they are most effective and best tolerated [2]. The word Chronopharmaceutics comprised of two words:

Chronobiology and Pharmaceutics. The term Pharmaceutics is the science of dosage form design in which the process of new chemical entity or old drugs converted into medications to be used safely and effectively. Chronobiology is the study of biological rhythms and their mechanisms [3].

Circadian rhythm:

Circadian rhythms are produced by natural factors within the body, but they are also affected by signals from the environment. Light is the main cue influencing circadian rhythms, turning on or turning off genes that control an organism's internal clocks. The term "Circadian" describes the biological rhythmic cycle which completes within span of single day. Our biological clocks drive our circadian rhythms. The biological clocks that control circadian rhythms are groupings of interacting molecules in cells are throughout the body. A "Master Clock" in the brain organizes all the body clocks so that they are in synchronization. A group of nerve cells which are consisted by Circadian Rhythms are regulated by "Master Clock".

These groups of nerve cell are called Suprachiasmatic Nucleus, or SCN [4]. Approximately 20,000 nerve cells of SCN are placed in the hypothalamus. Hypothalamus is the area of brain just above where the optic nerves arise from the eyes cross. Diagrammatic representation of biological clock in human is represented in the **Fig.1**. Natural components of humans and animals developed circadian rhythms; it is also accomplished from signals of the environment such as light and air which control genes of organism's internal clocks.

It is also regulated by sleep-wake cycles, hormone release, body temperature and other significant parameters on which body functions depend. It has also been associated to various sleep disorders such as insomnia etc. Abnormal Circadian Rhythms have also been associated with Obesity, Diabetes, Depression, Bipolar disorder and Seasonal Affective Disorder [5]. So why Circadian Rhythms are significant factors to view when administered the drugs to patients.

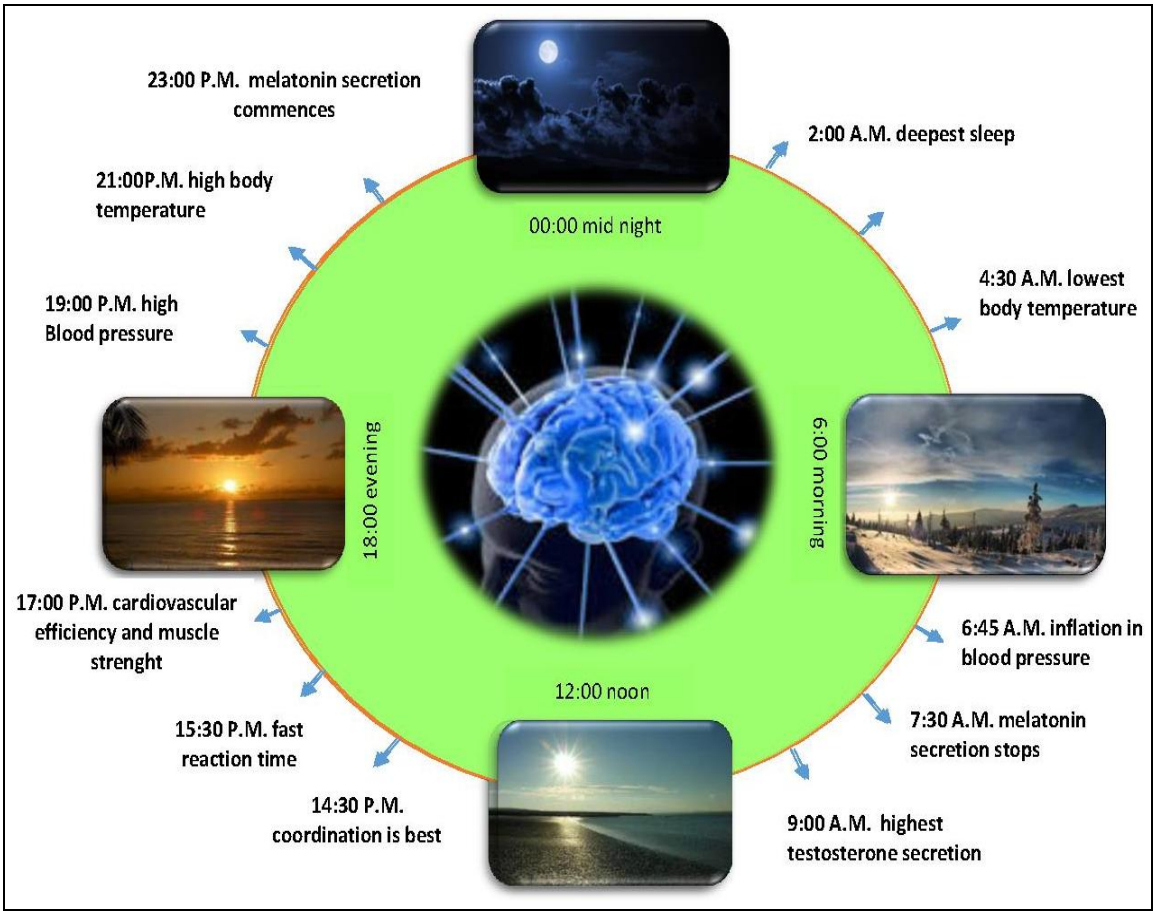

FIG.1: DIAGRAMMATIC REPRESENTATION OF BIOLOGICAL CLOCK IN HUMAN.

Classification of pulsatile drug delivery systems: There are many ways to classify the Pulsatile System according to the system formulated for the disease, type of products available in the markets and system used for various diseases. There are two types of Pulsatile System, Single unit systems and Multiple unit systems. Single unit systems are designed either as capsule based or osmosis based systems. Single unit systems are also designed according to the eroding/soluble or rupturable coating. In the case of Multiple unit system, the Pulsatile release is induced by changing the membrane permeability or by coating it with soluble, erodible or rupturable membrane. Classification on the basis of system release of the drug is represented in the **Fig. 2.**

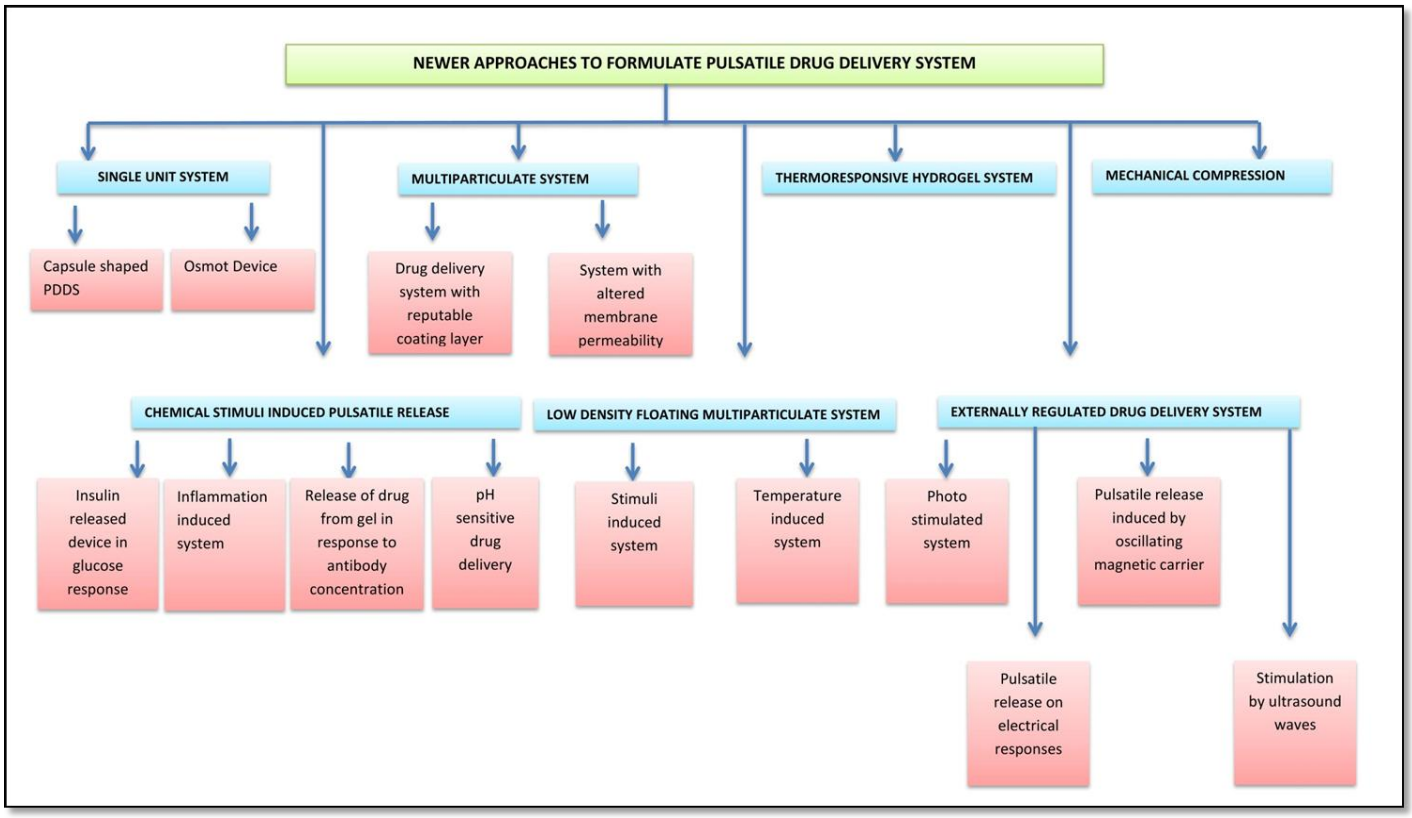

FIG.2: CLASSIFICATION OF PULSATILE DRUG DELIVERY SYSTEM

1. Single Unit System:

a. Capsular pulsatile drug delivery system:

This method includes pulsing cap system in which predetermined off time period is continued (lag time) by using a plug that is pushed by swelling or erosion[10]. As per the study by R.P. Scherer International Corporation, Michigan[11] developed the Pulsincap™ system, in which plug increasing the lag time and plug pushed away by swelling or erosion, when interacts with the soluble material. A swellable hydrogel plug was used to seal the drug contents into the capsule body. Drug releases from the capsular system when it comes in contact with the dissolution medium from the insoluble capsular body, the plug gets swell, after a lag time. Capsular body encloses a drug which acts as a reservoir. Lag time was controlled by the length and solubility of the plug and its point of insertion also decide the release rate (**Fig. 3**).

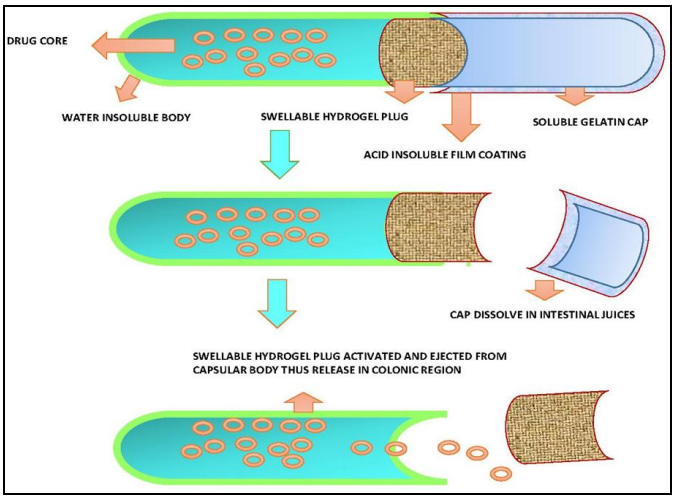

FIG. 3: FLOW CHART REPRESENTATION OF CAPSULAR PULSATILE DRUG DELIVERY SYSTEM.

b. Osmotic pulsatile drug delivery system:
This system is used in poorly water soluble drugs. Alza corporation developed a OROS® system, it consist a one or more drug layer which is coated by bilayer or trilayer core consisting of one push layer, so it also called push-pull system (Figure). The drug layer consists of three components such as poorly soluble drugs, osmotic agents and a suspending agent. Push layer comprised with an osmotic agent and water swellable polymers. Tablet core is coated by semipermeable membrane. Lag time depends on the amount of osmotic agent and thickness layers of semipermeable membrane.

Various systems are commercialized in market and available for patients for various diseases in which drug shows poor solubility e.g. Procardia XL® system are used for Hypertension, Ditropan XL system are used for to reduce muscle spasms of the bladder and urinary tract and Concreata® system are famous example of Osmotic Pulsatile drug delivery system. L-OROS® and SOFTCAP^{TM} both systems are recently produced by Alza corporation, in which combined features of a controlled release and bioavailability enhances delivery system to enhance compliance and therapeutic of the drug. The main advantage of this system is to overcome the drug solubility issue. OROS-CT® systems are used to target the drug locally to the colon for the treatment of disease. This is the single osmotic unit or may combine with 5 to 6 push-pull units. Each system is 4mm in diameter, encapsulated within a hard gelatin capsule.

c. Solubility modulation to single unit drug delivery system: This system is concerned osmotic drug delivery system containing a pulsatile release drug solubility modulator that monitored the solubility of the drug(s) across the system. This type of system is concerned to both a novel and utile drug delivery system a drug to an environment of use over a conditioned duration of time is easily accomplished. This process impacts the release profile of the drug from the device. Therefore, exact selection of the drug solubility modulator is allowing the release of drug to be monitored by the device. It is not monitored by the intrinsic water solubility of the drug or the environment surrounding the device as discussed in the previous system.

This system is controlled by the surfactants and solubility modulating agent. The other advantages of this system is to provide a method for converting unacceptable drug release in vitro profiles that have been recognized as therapeutically desirable. Solubility modulation by Single unit drug delivery system is promptly fabrication to deliver a predetermined dose of agent at a programmed rate from compositions of matter in the varied geometries and sizes of tablets, pellets, multi-particulates, and such related dosage forms as familiar to those skilled in the art of oral, buccal, vaginal, rectal, nasal, ocular, aural and related routes of administration.

The above stated method was developed for the administration of selective β2 agonist agent in the asthmatic patients for prompt relief from pain. The particular composition having an active ingredient or a modulating agent, later agent should present within composition in such amount which is less than maximum concentration, which maintains saturation in medium that enter osmotic device. The above system utilise drug solubility. Organic, inorganic salts and solid inorganic acids are some example of modulating compounds.

d) Osmotic system with expandable orifice:
Osmotic System with expandable orifice is based on the structure of the capsule itself rather than the osmotic agent, solubility modifier and chemical composition placed in the capsule. In this system, lag time depends on the structure of the capsular system. By forming the orifice in the wall section of the elastic material in osmotic system, creates the pulsatile release or initiate the drug release from the system through the orifice, which stretches in response to the osmotic pressure in system.

The orifice is sufficiently small to remain closed, or at least considerably closed, when the pressure is less than the threshold level and yet opening as the elastic material stretches when the osmotic pressure rises to the threshold level (**Fig. 4**). From the aqueous environment, capsule continuously absorbs the moisture; the absorbed moisture makes the pressure inside the capsule to rise until the level of threshold is achieved and at this time beneficial agent release from the orifice until the pressure is comfortably relieved to makes the orifice to

reclose. This cycle is repeated until the beneficial agent is consumed from the system or the capsule is moved out from the environment. This system having one major advantage, which enhances the performance of the device, movable partition which divides the capsule interior into two compartments, one for osmotic engine and other for beneficial agent, which distinct from the beneficial agent. Beneficial agent comprising the orifice at the capsular wall and during the travel, the partition will be at the beneficial agent. Osmotic agent compartment creates the pressure inside the capsule due to inward diffusion of water though the partition that keeps the contents of the two compartments from mixing.

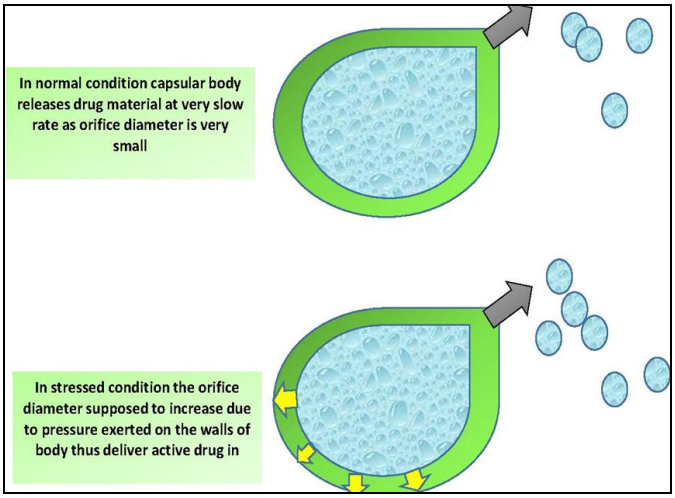

FIG. 4: REPRESENTATION OF EXPENDABLE ORIFICE TECHNIQUE

2. Multiparticulate System:

The multiplicity of small discrete units are combined in single oral dosage form are mainly called as Multiparticulate drug delivery system. Each discrete unit comprises of some specific characteristics. Multiparticulate systems are divided into plurality of subunit of dosage, mostly containing thousands of spherical particles with the diameter of 0.05-2.00 mm.

So it is a multiparticulate dosage forms are pharmaceutical formulations in which the active substance is present as a number of small independent subunits. To provide optimum total dose, these system containing subunits that are packed into an encapsulated or sachet or compressed into a tablet. It provides many advantages as compared to single-unit system due to their small size subunits. Due to their better results such as increased bioavailability, reduced risk of systemic toxicity, reduced risk of local irritation and predictable gastric emptying are commonly a subject of development of multiparticulate dosage form instead of single unit systems. These systems are also less dependent on the gastric emptying, ensuring less inter and intra parameter variance in gastrointestinal transit time. There are also many other advantages of developing a drug as a multiparticulate system such as to help disintegration in the stomach because its already subunits, to supply a convenient, fast disintegrating tablet which dissolves in water before swallowing which can aid compliance in older patients and children.

It shows better pharmacokinetic behaviour as compared to monolithic preparations. In modified multiparticulate pulsatile release system drug safety may also be increased. For example, comparison between monolithic and multiparticulate, if the film coat of single unit in the case of monolithic is damaged, which leads to complete dose will be released in the stomach, which causes pain or ulceration or reduced efficacy, depending on the reason choosing the protection of the enteric coating. Similarly in the case of multiparticulate dosage form, especially for modified release system, if the film coated is damaged, which leads to the release characteristics are integrated into every single subunit, which represents a small part of the total dose and providing the safety to the dose. Drug release mechanism from multiparticulate systems basically depends on three parameters such as diffusion, erosion and osmosis. Beside advantages, there are some disadvantages also such as low drug loading, proportionally higher need of excipients, large number of process variables and requirement of advanced technology, multiple formulation steps, adequate measure parameters, higher cost of production and skilled personnel to develop the formulations.

a. Drug delivery system by altering membrane permeability in a formulation:

Drug delivery system through altering membrane permeability in the formulation is based on the sigmoidal released pattern and it is beneficial for timed released and colonic drug delivery system.

Sigmoidal release pattern is established on the permeability and uptake of Eudragit RS or RL by water, regulated in the presence of dissimilar counter in the release medium. Narisawa et al. have built up a pulsatile device depending on the change in diffusion properties of Eudragit RS. They observed that a very slow release rate of theophylline coated with Eudraget RS in pure water but when the microcapsules were impressed in acid solution such as glutaric, acetic, tartaric, malic and citric or succinic acid, a major increase in the release rate was observed.

This is because of the higher hydration of the film comprising quaternary ammonium groups on interaction with acids, was not affected by succinic acid. When succinic acid was in integrated into the core of Eudragit RS coated theophylline beads, the drug release profile showed a typical sigmoidal pattern.In the case of acetaminophen contained product also showed the same results. Multiparticulate containing acetaminophen beads with different thickness of coating administered to beagle dogs and shows similar lag times in vivo and in vitro. Thickness of semipermeable decides the lag time; it is directly proportional to the thickness. Still, drug release profile was independent to the thickness but was affected by the amount of the salt in the system. It is concluded that, release mechanism is dependent on the permeability modifier or amount of the salt.

b) Drug delivery system using rupturable coating:

In this type of system coating ruptures or disintegrates to release a particular drug to the target. There are many reasons of rupturing of coat such as swelling, osmotic pressure, disintegration and effervescent recipient. In case of effervescent mixture which is usually contained in a mixture of citric acid and borax which is introduced into the core further coated with ethylcellouse. Pressure is created inside the body of the system which leads to rupturing of the coating due to the generation of carbon dioxide gas in the system. Lag time in this system is dependent on the thickness of coating and hardness of the core tablet. Many agents such as sodium starch glycollate and low substituted hydroxyl propyl cellulose are used as the swelling agents and when they come in contact with the GI fluid, leads to the complete rupture of the film which leads to the drug release from the system.

The Time clock system contained solid dosage form coated with lipid barrier such as carnauba wax and beeswax along with surfactants. When both these wax comes in interaction with aqueous medium, the coat emulsifies or erodes after the lag time. Gastrointestinal motility, pH, enzyme and gastric residence doesn't affect the lag time of the system. Viscosity grade and thickness of the polymer decides the lag time and onset action of the drug.

3. Low density floating multiparticulate sytem:

a. Stimuli induced system:

In case of low density floating multiparticulate system, biological environment induce the stimuli to release the drug by the system. Gels or micelles release the drug by the response from stimuli induced, which may deswell, swell or erode in the response to the respective stimuli. Biological factors such as temperature or other chemical stimuli induce the stimulation in the system and releases drug from it. Drug release mechanism is based on the ejection of the drug from the gel as the fluid phase syneresis out, drug diffusion along a concentration gradient, electrophoresis of charged drugs towards an oppositely charged electrode and liberation of the entrapped drug as the gel or micelle complex erode. This system releases the therapeutic agents in the presence of specific enzyme or protein. Reason of choice of this system is that this can be qualified according to the task to be achieved and having excellent drug delivery system.

b. Temperature induced system:

Temperature play an important role to deliver the medicines in the system at a particular time and location. The significance of temperature as a mediator has been rationalized by the fact that the body temperature usually deviates from the physiological temperature 37° C in the presence of pathogens or pyrogens. The variation in the temperature act as triggers to stimulate the drug to target the disease accompanying fever, such type of system also known as thermosensitive Pulsatile drug delivery system. The temperature-induced pulsatile/triggered drug delivery system apply

various polymer properties, including the thermally reversible coil/globule transition of polymer molecules, swelling change of networks, glass transition and crystalline melting. Mainly two type of systems work under the temperature induced system such as Thermoresponsive Hydrogel System and Thermoresponsive polymeric micelle system.

In Thermoresponsive Hydrogel System utilizes hydrogel which have reversible volume changes in reply to changes in temperature. Gel is made of liner polymer, which is follow at a transition temperature when gel shrinks at the lower critical solution temperature. Hydrogel have some specific characteristics to absorb the water from chemical attraction and swell at temperatures below the transition temperature whereas they shrink or deswell at temperature above the transition temperature by expelling water and in case of Thermo responsive Polymeric Micelle systems, due to its properties and biological interest, this is the best candidate as drug carrier for the treatment of cancer.

As the per the study of Kataoka and co-workers, it is observed that the polymeric micelle is build-up of amphiphilic block copolymers exhibiting a hydrophobic core with a hydrophilic corona, due to its unique characteristics, polymer micelles exhibit stealth characteristics and are not recognised by the body defence system (reticuloendothelial system; RES). Thus, passive targeting could be accomplished through an enhanced permeation retention (EPR) effect of the tumour sites. Pluronic®. Gels of this type of polymer display low viscosity at ambient temperature, and exhibit a sharp increase in viscosity as the temperature rises. Both systems are the best systems for Pulsatile Drug Delivery system when the medicament deliver through temperature induced system.

4. Chemical Stimuli Induced Pulsatile Release:

In Chemical Stimuli Induced Pulsatile Release system, therapeutic agent release in the presence of any biological factor such as enzyme, pH or any other chemical stimuli.

a. pH sensitive drug delivery: This system is based on the pH polymer properties to a specific location. This system based on the two components, first is immediate release of the drug and second is to control the release of drug by alter the pH. The fact which gave development to this delivery system is that there is an existence of varying pH environment at different Gastro Intestinal Tract areas. By analysing pH of specific location, one can select pH dependent polymer for delivering the drug in right amount to achieve optimum plasma concentration. Various types of pH dependent polymer are used in this system, Cellulose acetate phthalate, Sodium carboxy methyl cellulose and Eudragit E-100.

b. Insulin released device in glucose response:

These types of Pulsatile Drug Delivery system are used for diabetic patients for better compliance. This new approach to deliver an active drug in response to any stimulation that may be biological factor like enzyme, any endogenous substance. To supply insulin in the body is tedious job as it is different from other form of drugs. The glucose sensitive gel play a desperate role of self-controlling drug release in target tissue simultaneously regulating and separating system with glucose sensitivity. So its administration should be done with care and precaution to avoid any side effects. Exact amount should reach the target site according to the requirement of the treatment regimen. Glucose oxidase is an enzyme which catalyses the oxidation of glucose to gluconic acid.

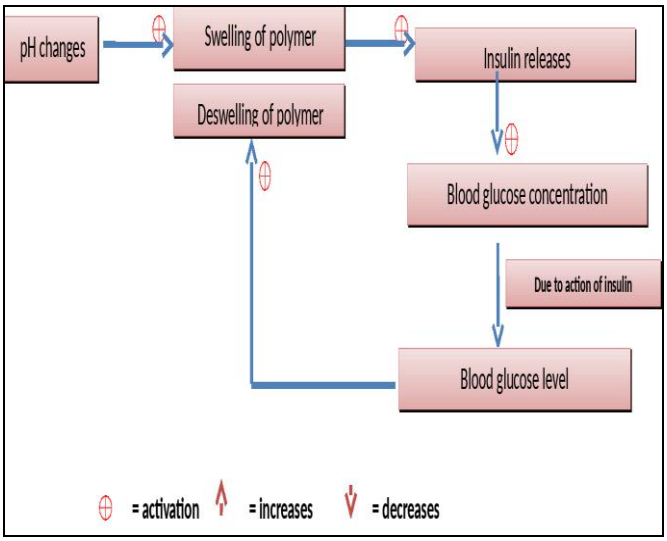

FIG 5: DIAGRAMMATIC REPRESENTATION OF EFFECT OF CHANGE IN pH ON INSULIN ACTIVITY USING FEEDBACK MECHANISM.

In an environment where glucose concentration is high, this oxidation lower the pH to 5.5 to 5.8 hence forth this enzyme is used in glucose sensing and create a new plausibility to formulate various types of pH sensitive hydrogels for modulating insulin drug delivery. Diagrammatic representation of effect of change in pH on insulin activity using feedback mechanism is explained in the **Fig.5**.

c. Release of drug from gel in response to antibody concentration:

Miyata and co-workers produced novel gels which reacted to alter the concentration of bioactive compound to change their swelling/deswelling characteristics. Antigen-antibody complex formation is of great importance as the cross-linking units in the gel due to such specific interaction, Reversible gel swelling/deswelling and drug permeation changes occurs by the utilization of the difference in association constants between polymerized antibodies and naturally derived antibodies towards specific antigens.

d. Inflammation induced pulsatile release:

Inflammation occurs due to physical or chemical stress such as injury, fracture etc. Hydroxyl radicals are produces after inflammation due to responsive cells. Yui and co-workers studied that hydroxyl radicals are used to deliver the drug in pulsatile manner. They used hyaluronic acid which is degraded by hyaluronidase or free radicals. Its degradation is very slow in normal state of health. But degradation via hydroxyl radicals is very dominant and rapid when hyaluronic acid is injected at inflammatory site. So, this is the best candidate to treat the patients with inflammatory diseases like Rheumatoid Arthritis, using anti-inflammatory drugs incorporated hyaluronic acid gels as new implantable drug delivery system.

5. Externally Regulated Drug Delivery System:

There is one more way to deliver drug by pulsatile manner that is through externally regulated system in which drug release is programmed by external stimuli like magnetism, ultrasound, electrical effect and irradiation.

a. Pulsatile released induced by oscillating magnetic carrier:

In magnetically regulated system, magnetic beads are contained in the implant. To achieve pulsatile drug delivery, there is an oscillating carrier which manages the drug release from the polymer. This carrier receives a stimulus to the magnetic field from incorporated materials like iron, cobalt and so on. The merits of type of release include some properties of magnetic carriers such as compatible, nontoxic, non-immunogenic and aqueous based. The approach behind this strategy is to attain slow rate of the drug through stomach and intestine at the specific position by an external magnet which alter time and extent of drug residence in stomach and colonic region. The diagrammatic representation of the mechanism of magnetic bead carrier is shown in the **Fig. 6**.

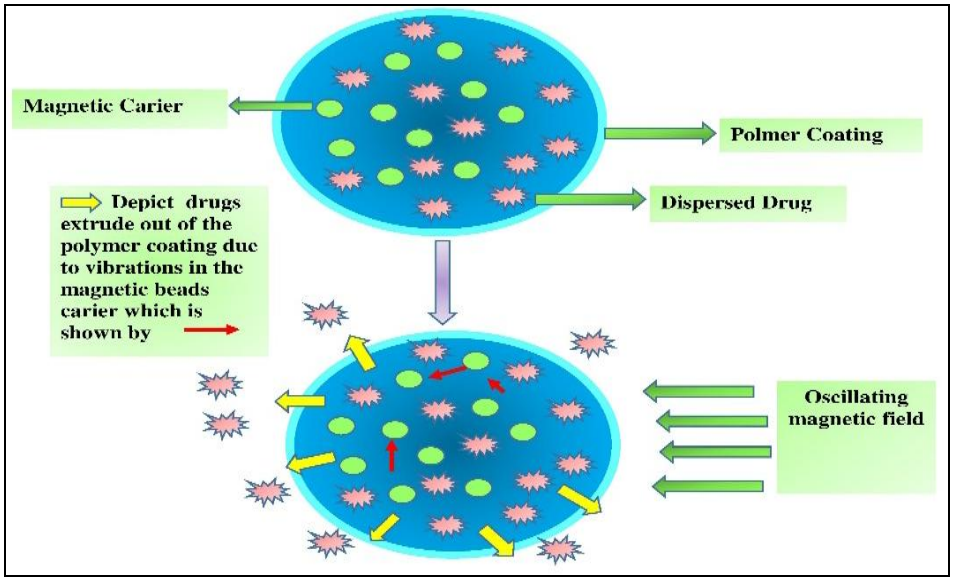

FIG. 6: SCHEMATIC DIAGRAM OF PULSATILE DRUG DELIVERY TECHNIQUE USING MAGNETIC BEAD CARRIER

b. Pulsatile release on electrical responses:
Microelectronic and micromachining are the novel developments and have a vital role in chronotherapy. These systems include sonophoresis, infusion pump and iontophoresis. Kishi et al. designed an electrically stimulated drug delivery system by utilising electrically stimulated swelling characteristics of polyhydrolic gels. These gel exhibit swelling and de swelling behaviour and response to an electrical stimulus. The active drug molecule within the gel may release out of the electrical stimuli induced gel. Pilocarpine containing microparticulate gel was formulated for testing this method.

c. Stimulation by ultrasound waves: Ultrasound waves enhance the drug permeability through biological carrier. Miyazika et al utilizes ultrasonic waves to achieve 27 fold increases in the release of an anticancer drug fluorouracil from ethylene and vinyl acetate matrix. The strength of ultrasonic wave is directly proportional to the amount of drug released.

Orally administered chronopharmaceuticals currently available in the market:
There are various products available in the markets, which is used for the many disease in pulsatile manner. Details of the currently available orally administered Chronopharmaceuticals in the markets are explained in the table with brand name and its rational use.

ORALLY ADMINISTERED CHRONOPHARMACEUTICALS CURRENTLY AVAILABLE IN THE MARKET

Brand Name	Drug	Name of the Manufacturer	Rational for use in chronotherapy
VERELAN PM®	Verpamil HCL	Recro Gainesville	Hypertension
INNOPRAN ® XL	Verapamil HCL, Propranolol HCL	Alza Corporation	Hypertension
DIFFUTAB®	Propranolol HCL	Alza Corporation	Management of both hypertension (high blood pressure) and angina pectoris (chest pain).
GEOCLOCK®	NSAIDs	SkyePharma	Rheumathoid Arthritis
GEOMATRIX™	Nisoldipine	SkyePharma	Hypertension
NAPRELAN®	Naproxen sodium	Alkermes Pharma Ireland Limited.	Rheumatoid Arthritis, Osteoarthritis, Analgesia
CARDIAZEM LA®	Diltiazem	Valeant Pharmaceuticals	Angina Pectoris Prophylaxis, Atrial Fibrillation, Atrial Flutter, and others.
INVEGA®	Paliperidone	Push-Pull System, Osmotic mechanism	Schizophrenia
PULSINCAP™	Dofetilide	MiddleBrook Pharmaceuticals, Inc.	Antiarrhythmic
MOXATAG™	Amoxicillin	MiddleBrook Pharmaceuticals, Inc.	Infection
UNIPHYL®	Theophylline	Purdue Pharma LP	Asthma

CONCLUSION: During the last two decades, pharmaceutical technology has grown leaps and bounds and, with the advent of pulsatile drug delivery, one can remain assured of accomplishment of goal for safe and effective therapy. The present review concludes that pulsatile drug delivery system is the newer technique which can overcome the conventional type of dosage forms like tablets, capsules, lozenges, syrups etc. These devices have plausibility to cure rare ailments by attaining 100% bioavailability of active biomolecule in plasma or blood. . These systems deliver the drug at right time, place and amount in the patient's body. The circadian disorders generally require chronopharmacotherapy, which can be easily accomplished by pulsatile drug delivery system in a very organized manner. The above study, that Circadian Rhythms play prominent role in the designing of this type device. This is a novel approach to reduce patient noncompliance and increasing drug target action in stipulated time.

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