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PULSATILE DRUG DELIVERY SYSTEMS: RECENT TECHNOLOGY

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ABSTRACT: Pulsatile Drug Delivery Systems are gaining a lot of interest as they deliver the drug at the right place at the right time and in the right amount, thus providing spatial and temporal delivery and increasing patient compliance. These systems are designed according to the circadian rhythm of the body. The principle rationale for the use of pulsatile release of the drugs is where a constant drug release is not desired. A pulse has to be designed in such a way that a complete and rapid drug release is achieved after the lag time. Various systems like capsular systems, osmotic systems, single- and multiple-unit systems based on the use of soluble or erodible polymer coating and use of rupturable membranes have been dealt with in the article. It summarizes the latest technological developments, formulation parameters, and release profiles of these systems. These systems are beneficial for the drugs having chronopharmacological behavior where night time dosing is required, such as anti-arhythmic and anti-asthmatic. Current review article discussed the reasons for development of pulsatile drug delivery system, types of the disease in which pulsatile release is required, classification, advantages, limitation, and future aspects of pulsatile drug delivery system.

INTRODUCTION: Over the last 30 years the pharmaceutical market has been demonstrated increasing preferably for controlled and targeted drug delivery system. Such systems have been focused on constant, variable; sustain drug release and/or targeting the therapeutic agent to a specific site/ tissue/organ. However, recently there are certain conditions for which such release pattern is not suitable. Such conditions that lead to the requirements of a time programmed therapeutic system, which capable of releasing drug after predetermined time delay and maintain constant drug levels throught the day. To introduce the concept of chronotherapeutics, it is important to define the following concepts.

Chronobiology [1]**:** Chronobiology is the science concerned with the biological mechanism of the diseases according to a time structure. “Chrono” pertains to time and “biology” pertains to the study, or science, of life.

Chronopharmacology [1]**:** Chronopharmacology is the science concerned with the variations in the pharmacological actions of various drugs over a period of time of the day.

Chronopharmacokinetics [1, 2]**:** Chronopharmacokinetics involves study of temporal changes in drug absorption, distribution, metabolism and excretion. Pharmacokinetic parameters, which are conventionally

considered to be constant in time, are influenced by different physiological functions displaying circadian rhythm. Circadian changes in gastric acid secretion, gastrointestinal motility, gastrointestinal blood flow, drug protein binding, liver enzyme activity, renal blood flow and urinary pH can play role in time dependent variation of drug plasma concentrations.

Chronotherapy [1]**:** Co-ordination of biological rhythms and medical treatment is called chronotherapy.

Chronotherapeutics [1, 3]**:** Chronotherapeutics is the discipline concerned with the delivery of drugs according to inherent activities of a disease over a certain period of time. It is becoming increasingly more evident that the specific time that patients take their medication may be even more significant than was recognized in the past.

Biological Rhythms [4]**:**

1. **Ultradian Rhythms:** Oscillations of shorter duration are termed Ultradian Rhythms (more than one cycle per 24 h). E.g.90 minutes sleep cycle.
2. **Infradian Rhythms:** Oscillations that are longer than 24 hours are termed as Infradian Rhythms (less than one cycle per 24hours). E.g. Monthly Menstruation.
3. **Circadian rhythms:** Circadian rhythms are self-sustaining, endogenous oscillations.

Diseases requiring Pulsatile Drug Delivery: Thorough understanding of the disease physiology is required before designing the pulsatile drug delivery system. A disease where rhythmic circadian organization of the body plays an important role, pharmacokinetics and/or pharmacodynamics of the drugs is not constant within 24 h. Table.1 enumerates various diseases showing such a chronological behavior.

Asthma is one such disease where pulsatile drug delivery system can be useful. Circadian changes are seen in normal lung function, which reaches a low point in the early morning hours. In case of cardiovascular diseases, several functions (e.g. BP, heart rate, stroke volume, cardiac output, blood flow) of the cardiovascular system are subject to circadian rhythms.

For instance, capillary resistance and vascular reactivity are higher in the morning and decrease later in the day. Platelet agreeability is increased and fibrinolytic activity is decreased in the morning, leading to a state of relative hyper coagulability of the blood **(Hermida et al., 2007).** Circadian variations of glucose and insulin in diabetes have been extensively studied and their clinical importance in case of insulin substitution in type 1 diabetes has been well exploited.

Furthermore, diverse directions of circadian changes in lipid fractions in patients and normal subjects may contribute to alteration in the rhythmicity of other metabolisms and in the blood coagulation system, thus leading to various complications. A circadian rhythm occurs during hepatic cholesterol synthesis. In case of arthritis there is a circadian rhythm in the plasma concentration of C- reactive protein and interleukin-6 of patients with Rheumatoid arthritis (Lemmer, 1991).

Advantages of Pulsatile Drug Delivery System: (Kamboj&oberoy,2009 and Rathod, 2007)

1. Extended day time night time activity.
2. Reduce side effects.
3. Reduced dosage frequency.
4. Reduction in dose size.
5. Improved patient compliance.
6. Lower daily cost to patient due to fewer dosage units is required.
7. Drug adapts to suit cardiac rhythms to body function or disease.
8. Drug targeting to specific site like colon.
9. Protecting of mucosa from irritating drugs.
10. Decreases drug interaction due to lower cytochrome P-450 isoenzymes

Limitations of Pulsatile Drugdelivery System: (Rathod, 2007)

1. Multiple manufacturing steps in case of Multiparticulate drug delivery system.
2. Low drug load.

3. Incomplete release.
4. *In vivo* variability in single unit pulsatile drug delivery system.
5. Drug dose manipulation in case of child and elder patients is not possible.
6. Immediate withdrawal

Recent advances in the Pulsatile Drug Delivery System: Nowadays pulsatile drug delivery systems are gaining importance in various disease conditions specifically in diabetes where dose is required at different time intervals. Among these systems, multi-particulate systems (e.g. pellets) offer various advantages over single unit which include no risk of dose dumping, flexibility of blending units with

Different release patterns, as well as short and reproducible gastric residence time **(Dashevsk &Mohamad, 2006).** Multiparticulate systems consists pellets of different release profile which can be of any type like time dependent, pH dependent, microflora activated system. Site and time specific oral drug delivery have recently been of great interest in pharmaceutical field to achieve improved therapeutic efficacy. Gastro retentive drug delivery system is an approach to prolong gastric residence time, thereby targeting site specific drug release in upper gastrointestinal (GI) tract.

Floating drug delivery system (FDDS) and bioadhesive drug delivery are widely used techniques for gastro retention. Low density porous multiparticulate systems have been used by researchers for formulation of FDDS. Sharma and Pawar developed multiparticulate floating pulsatile drug delivery system using porous calcium silicate and sodium alginate for time and site specific drug release of meloxicam **(Sharma & Pawar, 2006).**

Technologies used in Chronopharmaceutics: Major objective of chronopharmaceutics is to deliver the drug in higher concentrations during the time of greatest need and in lesser concentrations when need is less to minimize unnecessary side effects. Various technologies used in development of chrono-pharmaceutical drug delivery system are discussed below.

1. **CONTIN Technology:** In this technology cellulosic polymer is solvated with volatile polar solvent. The resulting solvated cellulose polymer is reacted with aliphatic alcohol to form molecular coordination complexes. The complex is used as a matrix in controlled release formulations since it has a uniform porosity that can be varied .This technique has been used in development of sustained release tablet of aminophylline, theophylline, morphine, and other drugs.
2. **Physico-chemical modification of API:** In this, a proprietary method is used to modify the physicochemical properties like solubility, permeability, partition coefficient of drug. The method is useful when it is approved that bioavailability of drug is affected by solubility and permeability. Physicochemical property can be altered by altering chemical structure, melting point, molecular weight. Chronotherapeutic system by this technique has been formulated for antihyperlipidemic statins and anti ulcerative agents.
3. **OROS Technology:** This technology uses osmotic agents to provide preprogrammed, controlled drug delivery to the gastrointestinal tract. This technology , especially the OROS® delayed push pull™system, also known as controlled onset extended release (COER)was used to design covera- HS® , a novel anti hypertensive product. This enables delay, overnight release of verapamil to prevent surge in BP in morning.
4. **CODAS Technology:** Chronotherapeutic oral drug absorption system (CODAS®) is multi particular system, dosed at bed time that delays drug release for 4-5 h. The delay is provided by non enteric coating of the drug loaded beads. The technique has been used in formulation of Verapamil extended release capsules Verelan® PM.
5. **CEFORM® Technology:** This technique helps in development of microspheres of uniform size and shape. It is based on “melt spinning” in which biodegradable polymer or bioactive agents combination is subjected to combination of temperature, thermal gradients, mechanical forces, flow, and flow rates during processing.

The microspheres can be used in tablet capsule, suspension, sachet form. It can also be coated for controlled release. The technique has been actually used to develop cardiazem®LA, 1day diltiazem chronotherapeutic drug delivery system.

6. **DIFFUCAPS® Technology:** By this technique, unit dosage form like capsule is prepared. It consists of one or more population of drug containing particles (beads pellets, granules etc.). The drug core may consist of an inert particle or alkaline buffer crystal (e.g. cellulose ethers) which is coated with hydrophilic API-containing film forming agents like HPMC, PVP etc.

   The drug core may also be prepared by granulating and milling or by extrusion and spheronization of polymer composition containing the API. Such a chronomodulated drug delivery system is discovered to provide plasma concentration- time profile, which mimic the circadian rhythm and cardiovascular disease severity. This technique has been used in formulating Innopran® XL containing Propranol for hypertension.

7. **Chronomodulated infusion pumps:** Infusion pumps available in market for chronomodulated drug application are Melodie®, Programmable synchromed®, Panomat®, V5 infusion and Rhythmic® pumps. The portable pumps are usually light weight (300-500 g) for easy portability and precision in drug delivery. In case of Insulin therapy, Implantable infusion pump containing insulin reservoir is placed surgically in subcutaneous tissue of abdomen in the left upper or lower quadrant.

   A catheter leads from the pump through the muscle layers into the peritoneal cavity, where it floats freely, and insulin delivery is by intra peritoneal route. This insulin containing reservoir is refilled once a month or every 3 months at physician's office by inserting needle through the skin into the pump. Doses adjustments are made by the patient in range established by Physician using radiotelemetry and an electronic device that is held over the pump.

   The advantages are that absorption is faster by peritoneum route because of large surface area that is well vascularized than subcutaneous injection.

   Glycemic control is improved. Drawback of it is catheter blockade which can reduce insulin delivery. Pumps are used in diseases like cancer and diabetes.

8. **TIMERx® Technology:** This technology uses combination of xanthan gum and locust bean gum mixed with dextrose. The physical interaction between these component works to form a strong binding gel in presence of water. Release of drug is controlled by rate of water penetration from GIT to the above mentioned gum matrix, which expands to form a gel and releases active drug substance.

   Release of drug from tablet can be controlled by varying the proportion of gums, together with third component, the tablet coating and tablet manufacturing process. Potential application of this technology is development of oral, CR opioid analgesic oxymorphone.

9. **THREE DIMENSIONAL PRINTING®:** By this technique it is possible to engineer devices with complicated internal geometries, varying densities, diffusivities and chemicals. Different type of complex oral drug delivery devices that have been fabricated using this technique are: immediate extended release tablets, pulse release, breakaway tablets, and dual pulsatory tablets.

   The same technique is basis of theriform® Technology. In this products may be designed on a computer screen as three dimensional models before actual implementation of their preparation process. This versatile technique may find chronotherapeutic application in future.

10. **Other CR erodible polymers:** Erodible polymers are widely used in chonomodulated drug delivery system. Drug was sealed inside insoluble capsule body by an erodible tablet made of an insoluble dibasic calcium phosphate and gel forming HPMC excipient.

In brief, by careful selection and combination of polymeric drug carrier of different erosion/ degradation kinetic, or by manipulating the interaction energy between the drug and the polymer, it is possible to control drug release according to requirement of biological rhythm of given disease state **(Youan, 2004).**

11. **Controlled-release microchip:** This microfabrication Technology has the potential to be used in design of chronomodulated drug delivery system. With a better control over drug release kinetic to match biological requirement.

12. **PULSYS™:** This technology was used to develop chronotherepeutic system for amoxicillin. The rationale for designing this system was that antibiotics are more effective against fast growing bacteria. On administering immediate release system, bacteria respond to it by going into dormant stage, while pulsatile system is more effective because pulses of drug release after a regular time interval do not allow bacteria to go into dormant stage. Preclinical studies have shown that approach of using Pulsatile systems is more effective (**Parmar *et al*., 2009).**

13. **Spheroidal Oral Drug Absorption System (SODAS):** This technology is based on the production of controlled release beads and it is characterized by its inherent flexibility, enabling the production of customized dosage forms that respond directly to individual drug candidate needs. SODAS can provide a number of tailored drug release profiles, including immediate release of drug followed by sustained release to give rise to a fast onset of action, which is maintained for 24 hours.

    However, the opposite scenario can be achieved where drug release is delayed for a number of hours. An additional option is pulsatile release, where a once daily dosage form can resemble multiple daily doses by releasing drug in discrete bursts throughout the day **(Dvane *et al.,* 2009).**

14. **The Intestinal Protective Drug Absorption System (IPDAS):** This Technology is a high density multiparticulate tablet technology, intended for gastrointestinal irritant compounds. The IPDAS® technology is composed of numerous high density controlled release beads, which are compressed into a tablet form. Once an IPDAS® tablet is ingested, it rapidly disintegrates and disperses beads containing a drug in the stomach, which subsequently pass into the duodenum and along the gastrointestinal tract in a controlled and gradual manner, independent of the Feeding state.

    Release of active ingredient from the multiparticulates occurs through a process of diffusion either through the polymeric membrane and or the micro matrix of polymer/active ingredient formed in the extruded or spheronized multiparticulates.

    The intestinal protection of IPDAS® technology is by virtue of the multiparticulate nature of the formulation, which ensures wide dispersion of irritant drug throughout the gastrointestinal tract. Naprelan®, which is marketed in the United States and Canada, employs the IPDAS® technology. This innovative formulation of naproxen sodium is a novel controlled release formulation indicated for the treatment of acute and chronic pain **(White *et al.,* 1997).**

15. **GEOCLOCK® Technology:** Geoclock® tablets have an active drug inside an outer tablet layer consisting of a mixture of hydrophobic wax and brittle material in order to obtain a pH-independent lag time prior to core drug delivery at a predetermined release rate. This dry coating approach is designed to allow the timed release of both slow release and fast release active cores by releasing the inner tablet first after which the surrounding outer shell gradually disintegrates. Skye Pharma has used this novel technology to develop Lodotra™, rheumatoid arthritis drug, which delivers the active pharmaceutical ingredient at the most suitable time of day to treat the disease condition **(Venketesh, 2005).**

TABLE 2: MARKETED TECHNOLOGIES OF PULSATILE DRUG DELIVERY

Technology	Mechanism	Proprietoy name and dosage form	API	Disease	Reference
CODAS®	Multiparticular pH dependent system	Verelan®PM;XL release capsule	Verapamil HCl	Hypertension	(Panoz & Geoghegan, 1989)
DIFFUCAPS®	Multiparticulate System	Innopran®; XL Tablets	Verapamil HCL, Propranolol HCl	Hypertension	(Percel etal., 2002)
Three dimensional	Externally regulated system	TheirForm®	Diclofenac HCl	Inflammation	(Katstra et al., 2000)
PulsincapTM	Rupturable system	PulsincapTM	Dofitilide	Hypertension	(Stevens et al., 2002)
CONTIN®	Extended release tablet	Uniphyl®	Theophylline	Asthma	(Youan,2004; Mandal *et al.,* 2010)
OROS®	Tablet	Invega™	Paliperidone T	Schizophrenia	(Mandal *et al.,* 2010)
CEFORM®	Extended Release tablet	Cardiazem® LA	Diltiazem HCl	Hypertension	Youan,2004; Mandal *et al.,* 2010)
Physico-chemical modification of API	tablet	Pepcid®	Famotidine	Ulcer	(Youan,2004; Mandal *et al.,* 2010
Physico-chemical modification of API	Tablet	Zocor®	Simvastatin	Hypercholesterolemia	(Youan,2004; Mandal *et al.,*2010)
PROCARDIA XL®	Sustained release	Procardia XL	Nifedipine	Hypertension	(Youan,2004)

Need for Pulsatile Drug Delivery System: All endogenous biological processes and functions are programmed in time during the 24 hour for the conduct of specific activities at discrete times. A number of diseases show their pathognomonic following a biological rhythm;

1. **Asthma:** Circadian changes are seen in normal lung function, which drops in the early morning hours. The decreased lung function is more pronounced in people with asthma **(Janugade *et al.,* 2009).** It is usually highest at 4 pm and lowest at 4 am. It is the 4 am when asthma is more prevalent **(Qureshi *et al.,* 2008).**

2. **Arthritis:** Patients with osteoarthritis tend to have less pain in the morning and more at night, while those with rheumatoid arthritis, have pain that usually peaks in the morning and decreases throughout the day. Pro inflammatory cytokines exhibit a peculiar rhthmicity, in particular serum, TNF and serum IL-6, and together with other relevant immunological parameters display an elevation in early morning hours in patients with rheumatoid arthritis. Hence, such patients experience joint pain, morning stiffness and functional disability in early morning hours. Chronotherapy for all forms of arthritis using NSAIDs should be timed to ensure that highest blood level of drug coincide with the peak pain **(Cutolo *et al.,* 2008).**

3. **Duodenal Ulcer:** Gastric acid secretions are highest at night. Suppression of nocturnal acid is an important factor in duodenal ulcer healing, once daily bed time dosage regimen is recommended for H2 antagonists **(Roy *et al.,* 2009)**

4. **Cancer:** Chemotherapy may be more effective and less toxic if anticancer agents are administered keeping in mind the tumor cell cycles. This way it will be less toxic to normal tissue. Blood flow to tumors and tumor growth rate are each up to three fold greater during each daily activity phase of circadian cycle than during daily rest phase. Chronotherapy concept offers promise for improving current cancer treatment options.

However chronotherapy is still uncommon, limited to only 50 cancer centers throughout world. For chronotherapy to be widely accepted additional randomized clinical trials is needed to be conducted **(Ross *et al.*, 2006; Levi *et al.*, 2007; Ishida, 2007; Atilla *et al.*, 2009).**

5. **Diabetes:** Circadian behavior in glucose and insulin secretion in diabetes was revealed and studied. Increase in blood sugar level is found after meal **(Zvonic *et al.*, 2006; Aaron *et al.*, 2008; Haus, 2007).**

6. **Hypercholesterolemia:** Hepatic cholesterol synthesis is also found to follow circadian rhythm. But the rhythmicity varies according to individuals. There is a large difference in plasma mevalonate concentration between individuals. However cholesterol synthesis is generally higher during the night than during daylight. Diurnal synthesis is only 30-40% of daily cholesterol synthesis. Maximum production occurs early in the morning i.e. 12 hours after the last meal. The evening dose of HMG CoA reductase inhibitors is more effective than morning dose **(Ishida, 2007).**

7. **Neurological Disorder:** Investigation on epilepsy and convulsion demonstrate chronological rhythm. It is mentioned that brain area with highest concentration in noradrenergic nerve terminals and noradrenalin have a circadian rhythm in their content of noradrenalin **(Hofstra *et al*., 2008; Fred *et al.*, 2001).**

8. **Cardiovascular Diseases:** Angina pectoris, ventricular arrhythmia, acute myocardial infarction, sudden cardiac death, stroke, fatal pulmonary embolism, and hypertensive crisis's all are most frequent in morning as are other cardiovascular conditions. Cardiovascular events in a diurnally active person achieves peak in between 6 am to noon **(Francesco *et al.*, 2007; Izzedine *et al.*, 2006; Lemmer, 2006; Smolensky, 1996; Piccione *et al.*, 2005; Pasic *et al.*, 1998).**

The Conditions that Demand Pulsatile Release Include:

Many body functions that follow circadian rhythm i.e. their waxes and wanes with time. Ex: hormonal secretions.

- Diseases like bronchial asthma, myocardial infarction, angina pectoris, rheumatoid diseases, ulcer and hypertension display time dependence.
- Drugs that produce biological tolerance demand for a system that will prevent continuous present at the bio phase as this tend to reduce their therapeutic effect.
- The lag time is essential for the drugs that undergo degradation in gastric acidic medium (ex: peptide drugs) irritate the gastric mucosa or induce nausea and vomiting.
- Targeting to distal organs of GIT like the colon requires that the drug release is prevented in the upper two-third portion of the GIT.

All of these conditions demand for a time-programmed therapeutic scheme releasing the right amount of drug at the right time. This requirement is fulfilled by pulsatile drug delivery system, which is characterized by a lag time that is an interval of no drug release followed by rapid drug release [5]. Pulsatile systems are basically time-controlled drug delivery systems in which the system controls the lag time independent of environmental factors like pH, enzymes, gastrointestinal motility, etc.

TABLE 1: DISEASES REQUIRING PULSATILE DRUG DELIVERY

Disease	Chronological behavior	Drugs used
Peptic ulcer	Acid secretion is high in the afternoon and at night	H2 blockers
Asthma	Precipitation of attacks during night or at early morning hour	β2 agonist, Antihistaminic
Cardiovascular diseases	BP is at its lowest during the sleep cycle and rises steeply during the early morning awakening period	Nitroglycerin, Calcium channel blocker, ACE inhibitors, β Blockers etc.
Arthritis	Pain in the morning and more pain at night	NSAIDs, Glucocorticoids
Diabetes mellitus	Increase in the blood sugar level after meal	Sulfonylurea, Insulin, Biguanide
Attention deficit syndrome	Increase in DOPA level in afternoon	Methylphenidate
Hypercholesterolemia	Cholesterol synthesis is generally higher during night than during day time	HMG CoA reductase inhibitors

Methodologies for Pulsatile Drug Delivery [12, 13, 14, 15]:

Methodologies for the pulsatile drug delivery system can be broadly classified into three classes;

1. Time controlled
2. Stimuli induced
3. Externally regulated

Time controlled Pulsatile Release System: In time controlled drug delivery systems pulsatile release is obtained after a specific time interval in order to mimic the circadian rhythm. Such type of pulsatile drug delivery system contains two components: one is of immediate release type and other one is a pulsed release type.

Various methodologies that can be used for time controlled pulsatile release systems are following:

1. **Delivery systems with Rupturable Coating Layer:**

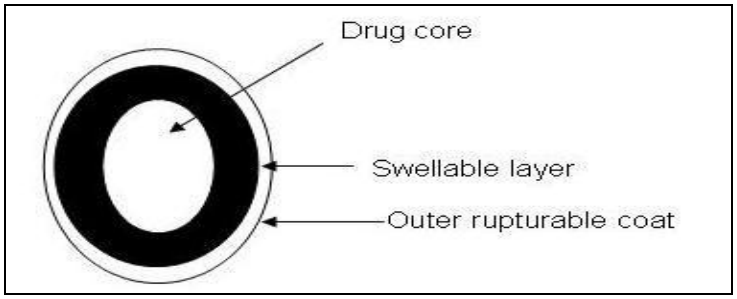

FIG. 1: SCHEMATIC DIAGRAM OF DELIVER SYSTEMS WITH RUTPURABLE COATING LAYER

These systems consist of an outer release controlling water insoluble but permeable coating subject to mechanically induced rupture phenomenon. Recently different systems based on hard gelatin capsules and tablet core were described, all coated by inner swellable and outer rutpurable layer. The film rupture may be attained by including swelling, osmotic effervescent additives in the reservoir **(Krogel & Bodmeier, 1999).** By optimizing the system, drug release can be obtained at specific time interval.

2. **Delivery systems provided with Erodible Coating Layers:**

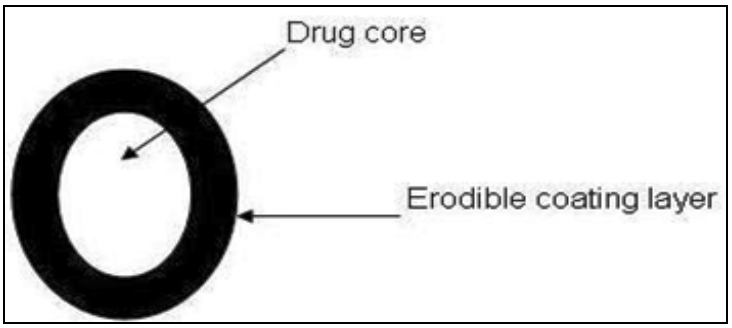

FIG. 2: SCHEMATIC DIAGRAM OF DELIVERY SYSTEMS WITH ERODIBLE COATING LAYERS

In such systems, the drug release is controlled by the dissolution or erosion of the outer coat which is applied on the core containing drug. Time dependent release of the active ingredient can be obtained by optimizing the thickness of the outer coat **(Gazzaniga et al., 2007).**

3. **Capsule shaped system provided with Release Controlling Plug:** These systems contain release controlling plug between immediate release compartment and pulsed release compartment. On contact with aqueous fluids, the cap rapidly dissolves thereby releasing the immediate release component followed by pulsed release component. The lag time is provided by the plug which is inserted in to the body.

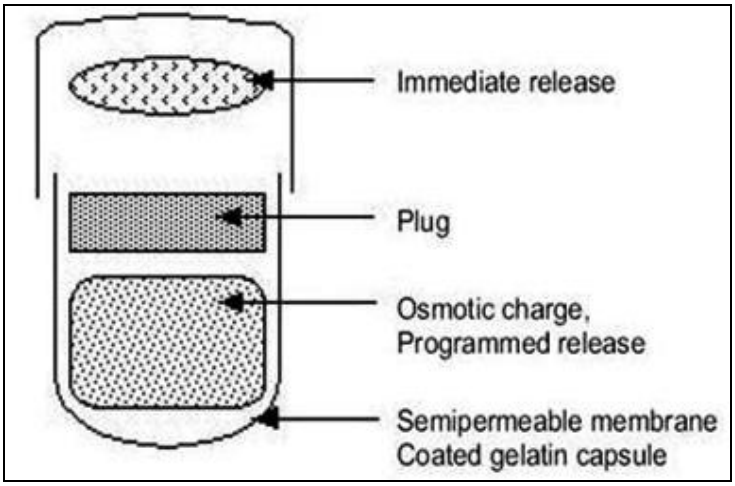

FIG. 3: SCHEMATIC DIAGRAM OF CAPSULE SHAPED SYSTEM PROVIDED WITH RELEASE CONTROLLING PLUG

4. **Stimuli induced Pulsatile Systems:** In these systems there is release of the drug after stimulation by any biological factor like Temperature or any other chemical stimuli **(Youan, 2004).** These systems are further classified as:

(i) **Temperature induced systems:** Thermo-responsive hydrogel systems have been developed for pulsatile release. In these systems the polymer undergoes swelling or deswelling phase in response to the temperature which modulate drug release in swollen state(Kikuchi & Okano, 2002). Y.H. Bae et al developed indomethacin pulsatile release pattern in the temperature ranges between 200C and 300C by using reversible swelling properties of copolymers of N-isopropylacrylamide and butyrylacrylamide (Bae et al., 1987).

(ii) **Chemical stimuli induced pulsatile system:**

i. **Glucose-responsive release devices:** In case of diabetes mellitus there is insulin rhythmic increase in the levels of glucose in the body requiring injection of the insulin at proper time. Several systems have been developed which are able to respond to changes in glucose concentration. One such system includes pH sensitive hydrogel containing glucose oxidase immobilized in the hydrogel. When glucose concentration in the blood increases glucose oxidase converts glucose into gluconic acid which changes the pH of the system. This pH change induces swelling of the polymer which results in insulin release.

Insulin by virtue of its action reduces blood glucose level and consequently gluconic acid level also gets decreased and system turns to the deswelling mode thereby decreasing the insulin release. Examples of the pH sensitive polymers includes *N,N*dimethylaminoethyl methacrylate, chitosan, polyol etc.

(iii) **Inflammation-induced Pulsatile Release:** On receiving any physical or chemical stress, such as injury, fracture etc., inflammation take place at the injured sites. During inflammation, hydroxyl radicals are produced from these inflammation responsive cells .Yui and co-workers focused on the inflammatory induced hydroxyl radicals and designed drug delivery systems, which responded to the hydroxyl radicals and degraded in a limited manner. They used hyaluronic acid (HA) which is specifically degraded by the hyaluronidase or free radicals. Degradation of HA via the hyaluronidase is very low in a normal state of health. Degradation via hydroxyl radicals however, is usually dominant and rapid when HA is injected at inflammatory sites. Thus, it is possible to treat patients with inflammatory diseases like rheumatoid arthritis; using anti-inflammatory drug incorporated HA gels as new implantable drug delivery systems **(Yui et al., 1992).**

(iv) **Drug release from Intelligent Gels responding to Antibody Concentration:** There are numerous kinds of bioactive compounds which exist in the body. Recently, novel gels were developed which responded to the change in concentration of bioactive compounds to alter their swelling/deswelling characteristics. Special attention was given to antigen-antibody complex formation as the cross-linking units in the gel, since such interactions are very specific. Utilizing the difference in association constants between polymerized antibodies and naturally derived antibodies towards specific antigens, reversible gel swelling/deswelling and drug permeation changes occurs **(Miyata et al.,1999).**

(v) **pH sensitive Drug Delivery System:** Such type of pulsatile drug delivery system contains two components one is of immediate release type and other one is pulsed release which releases the drug in response to change in pH. In case of pH dependent system advantage has been taken of the fact that there exists different pH environment at different parts of the gastrointestinal tract. By selecting the pH dependent polymers drug release at specific location can be obtained. Examples of pH dependent polymers include cellulose acetate phthalate, polyacrylates, sodium carboxy methylcellulose. These polymers are used as enteric coating materials so as to provide release of drug in the small intestine.

(vi) **Externally regulated systems:** For releasing the drug in a pulsatile manner, another way can be the externally regulated. Systems in which drug release is programmed by external stimuli like magnetism, ultrasound, electrical effect and irradiation **(Pozzi et al., 1994).**

Magnetically regulated system contains magnetic beads in the implant. On application of the magnetic field, drug release occurs because of magnetic beads. Saslawski *et al*. developed different formulation for in vitro magnetically triggered delivery of insulin based on alginate spheres **(Saslawski et al., 1988).** In case of ultrasonically modulated systems, ultrasonic waves cause the erosion of the polymeric matrix thereby modulating drug release.

Miyazaki *et al*., evaluated the effect of ultrasound (1 MHz) on the release rates of bovine insulin from ethylene vinyl alcohol copolymer matrices and reservoir-type drug delivery systems in which they found sharp drop in blood glucose levels after application of ultrasonic waves **(Miyazaki et al., 1988).**

Current situation and Future Scope: Now a day's pulsatile drug delivery is gaining popularity. The prime advantage in this drug delivery is that drug is released when necessity comes. As a result chance of development of drug resistance which is seen in conventional and sustained release formulations can be reduced. Furthermore, some anticancer drugs are very toxic.

These drugs give hazardous problems in conventional and sustained release therapies. Now many FDA approved chronotherapeutic drugs are available in the market. This therapy is mainly applicable where sustained action is not required and drugs are toxic. Key point of development of this formulation is to find out circadian rhythm i.e. suitable indicator which will trigger the release of drug from the device. Another point is absence of suitable rhythmic biomaterial which should be biodegradable, biocompatible and reversibly responsive to specific biomarkers in rhythmic manner.

Regulatory is another big question. In pre approval phase it is sometimes difficult to show chrono-therapeutic advantage in clinical settings. In post approval phase causal recreational drug abuse along with on a much larger scale, by the criminal diversion of these modified formulations for profit have arisen problems. The FDA has now heavily relied on the development and implementation of risk management programs as a strategy to allow an approval of a drug to go forward while exercising some restrictions. Many researches are going on the pulsatile drug delivery to discover circadian rhythm with suitable device in the world. In future this delivery will be a leading way to deliver therapeutic agents due to its some unique characters like low chance of dose dumping, patient compliance and the above factors [20].

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