# CHRONOMODULATED DRUG DELIVERY SYSTEM; A REVIEW

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## ABSTRACT:-

Chronomodulated drug delivery are lot of interest as they deliver the drug at the right site of action, at the right time and in the right amount which provides more benefits and to increasing patient compliance. It is time and site specific drug delivery system and thus provides spatial and temporal delivery. In these system in which the release of drug in the body is allowed to match with circadian rhythm of the disease, such as asthma, peptic ulcer, cardiovascular disease,arthritis,hypercholesterolemia.This system is programmed drug delivery system in harmonization with body clock. The pulse has to be designed in such a way that a complete and rapid drug release is achieved after the lag time. Pulsatile release is also useful for the targeting of drug irritating the stomach or degradable, as well for drugs developing biological tolerance or with an extensive first pass metabolism. Current review article discussed the reasons for the development of chronomodulated drug delivery system, advantage, limitations, type of disease in which the pulsatile release is required, methodologies, and recent advances in chronomodulated drug delivery system.

**KEYWORDS:-**Chronomodulated, lag time, disease, pulsatile release

## INTRODUCTION:

Over the last few years, controlled and targeted drug delivery have been dominating over the conventional dosage form. Such system has been concentrated on constant, variable; and sustain drug delivery system targeting specific site. However some disease symptoms occur during specific time of day or night so conventional dosage form are not able to fulfill necessities of condition. Modified release dosage form preparation to provide reduce dosing frequency improved patient compliance. There are several problem regarding modified dosage form such as resistance drug tolerance and the activation of physiological systems due to long term constant drug concentration in the body. So the chronomodulated dosage forms has been met for drug delivery. Chronomodulated system are lot of interest as they de liver the drug at right site of action, right time and in the right amount and thus provide to increasing patient compliance. This system based on the circadian rhythm of the body and the release of the drug as a pulse after a lag time has to be developed in such a way that a complete and rapid drug release follows the lag time. These system are called chronmodulated drug delivery system. Such system are also called as pulsatile drug delivery system. [1, 2]

Chronomodulated drug delivery system is to formulate for drug release conditions in various disease like cardiovascular disease like cardiovascular disease, diabetes mellitus, asthma, arthritis, peptic ulcer etc. In case of chronomodulated drug delivery system aims to release drug on programmed pattern i.e., at appropriate time and at appropriate site of action.

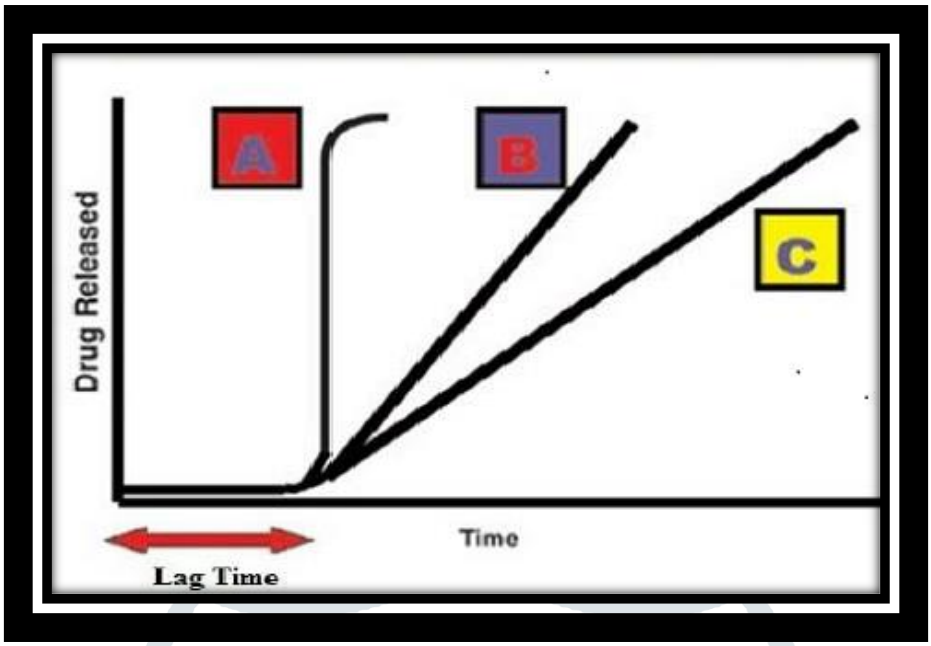


**Figure 1: A**=Release of drug as a "pulse" after a lag time (single pulse)

**B**=Delivering the drug rapidly and completely after a "lag time"

**C**= Constant drug release over a prolonged period of time after a "lag time"

The first pulsed delivery formulation that release the active substance at a precisely defined time point. It is called sigmoidal release. Thus the major challenge in the development of pulsatile drug delivery system is to achieve a rapid drug release after a lag time often the drug is released over an extended period of time also achieved.[3]

**Chronopharmacotherapy: -** It is timed drug therapy for drug administration is synchronized with biological rhythms and to produce maximal therapeutic effect and minimum harm for the patient. It consist of two words chronobiology and pharmaceutics.

**Chronobiology: -** It is the study of biological rhythms mechanism of the disease based to time structure. There are three types of mechanical rhythms in our body are-

**1) Circadian:-"**Circa "means about and "dies"means day and the oscillation that occur with the periodicity.

**2) Infradian Rhythm:**-Oscillation of longer duration the 24 hr. is termed as infradian rhythm(less than one cycle per day).E.g. Monthly menstruation

**3) Ultradian:**-Oscillation of shorter duration is termed as ultradian (more than one cycle per 24 h).

**Pharmaceutics:-**It is the discipline of pharmacy deals with the process of turning a new chemical entity (NCE) into medication to be used for safety and effectively by patient and it is also called science of dosage form developed.[4,5]

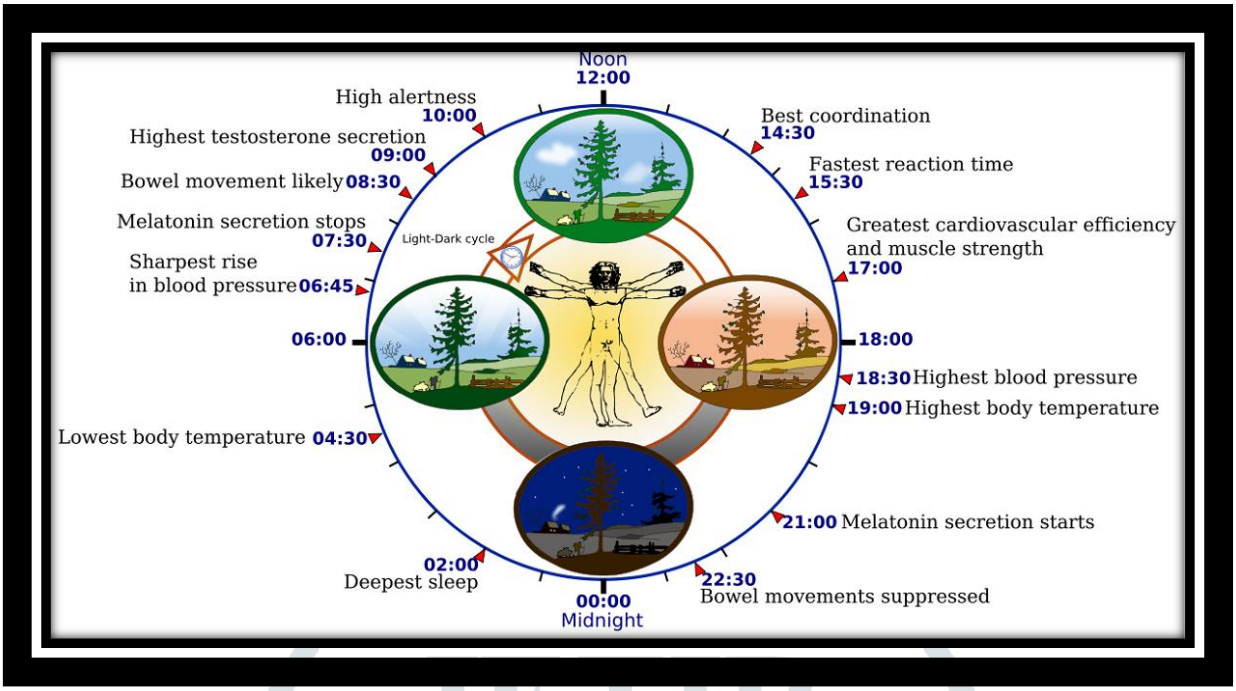


**Figure 2: Cycle of circadian rhythm**

**Necessities of chronomodulated drug delivery system:-[6, 7]**

1) First pass metabolism E.g.-beta blockers,Salicylamides
2) Chronopharmacotherapy disease
- Asthmatic attacks during early morning.
- Heart attacks in the middle of the night.
- Morning stiffness in arthritis
- Peptic ulcer during afternoon and night.

3) For which the tolerance is rapidly exists.E.g.-Biological tolerance
4) For targeting specific site in intenstine.E.g.-Colon
5) For time programmed administration of hormone and drugs.
6) Gastric irritation or drug instability in gastric fluid.E.g-Peptide drug

**Advantages:-[8, 9,10]**

1) Improved patient compliance
2) Reduced side effect
3) Reduced dosage frequency
4) Improve bioavailability
5) To achieve a unique release pattern
6) Improved stability
7) Drug adapts to suit circadian rhythm of body function or disease
8) Drug loss is prevented by extensive first pass metabolism
9) Reduce dose size
10) Limited risk of local irritation

**Limitation:-[11, 12]**

1) Multiple manufacturing step
2) Trained personal required for manufacturing
3) High cost of manufacturing
4) Incomplete release of drug
5) Process variable are high

## Disease required for chronomodulated drug delivery system:-[13,14]

Disease requiring by chronomodulated deliver system are asthma, arthritis, cardiovascular disease, diabetes mellitus, hypercholesterolemia and peptic ulcer. Such disease have predictable cyclic rhythms of the body is play an important role, pharmacokinetics and /or pharmacodynamics of the drug is not constant within 24 hr. Asthma is one of the such disease for chronomodulated drug delivery system can be useful.

**Table 1:-Disease required for chronomodulated drug delivery**

| Disease | Chronological Behavior | Drug used |
|---|---|---|
| **Asthma** | Precipitation of attack during night or at early morning hour. | $\beta_2$ agonist, antihistaminic |
| **Arthritis** | Pain in the morning and more pain in night. | NSAIDS,glucocorticoids |
| **Cardiovascular disease** | BP is at the lowest during the early morning awakening time. | Nitroglycerine, Calcium channel blocker, ACE inhibitors |
| **Diabetes mellitus** | Increase in blood sugar level after meal. | Sulfonyl urea,biguanide,insulin |
| **Hypercholesterolemia** | Cholesterol synthesis is generally higher during night time than during day time. | HMG CoA reductase inhibitor |
| **Peptic ulcer** | Acid secretion is high in the afternoon and in the night. | $H_2$ blockers |

## Methodologies for chronomodulated drug delivery system:-[15]

Chronomodulated drug delivery system can be broadly classified into three class:

I) Time controlled drug delivery system

II) Stimuli induced chronomodulated drug delivery system

III) Externally regulated chronomodulated drug delivery system

### I. TIME CONTROLLED PULSATILE DRUG DELIVERY SYSTEM

**A. Single unit pulsatile drug delivery system**

1. Capsule based system
2. Osmosis based system
3. Solublization or erosion system
4. System with rupturable coating membrane

**B. Multiparticulate/ Multiple Unit System**

1. Rupturable coating based system
2. Osmotic-based rupturable coating system
3. Chronomodulated delivery system by changes in membrane permeability

**II. STIMULI INDUCED PULSATILE DRUG DELIVERY SYSTEM**

**A) Temperature induced system**

1) Thermo responsive hydrogel system

**B) Chemical stimuli induced Pulsatile system**

1) pH sensitive drug delivery system

2) Glucose response insulin release device

3) Inflammation induced system

4) Enzymatically activated liposomes

**III. EXTENLLY REGULATED PULSTILE DRUG DELIVERY SYSTEM**

A) Magnetically induced system
B) Electrically induced system
C) Ultrasonically induced system
D) Photo induced system

## I.TIME CONTROLLED PULSATILE DRUG DELIVERY SYSTEM

**A) Single unit system**

**1) Capsule based system: -** These system consist of pulsincap system have been developed. Such system consist of an insoluble capsule body containing a drug and plug. The plug may be erodible, swelling or soluble and the lag time is controlled by plug in which pushed away by swelling or erosion and drug is release as a pulse from the insoluble capsule i.e. “Pulsincap”.

- The Pulsincap® system is an example of a system and it is made up of water insoluble capsule body filled with the drug. Hydrophilic polymer are used for plugs like hydroxypropylcelluose, polyvinyl-acetate, pectin etc. Most of the drug have been formulated in the form of pulsincap system for hypertension, angina, peptic ulcer etc. Weight amount of the hydrophilic swellable polymer such as HPMC or guar gum was placed on the top and compressed slightly using a rod to form compact plug.[16,17]

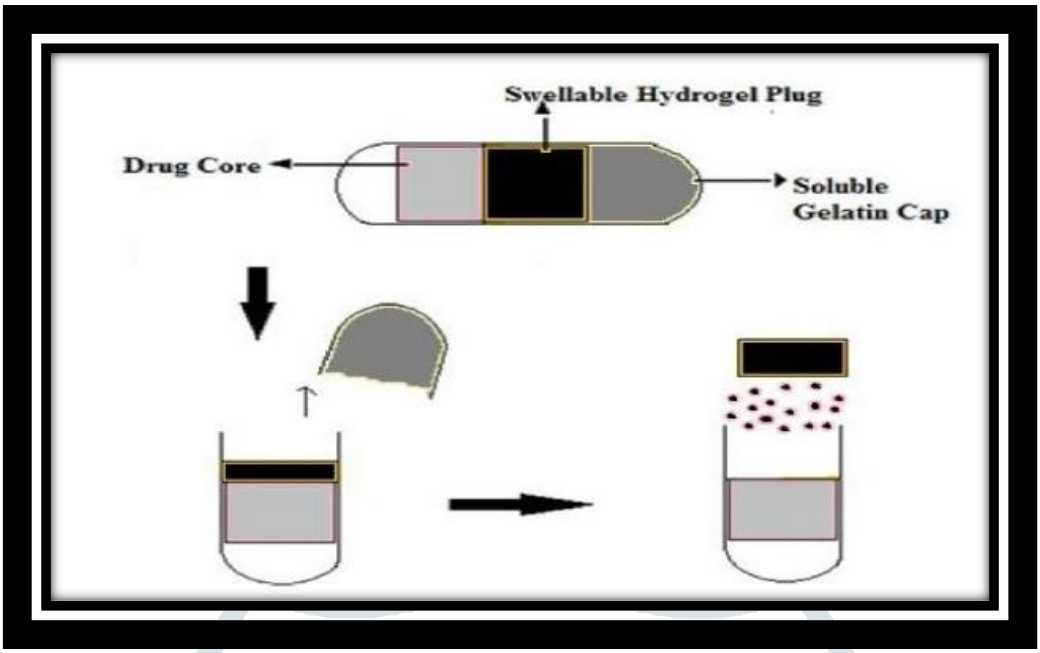


**Figure 3: Design of Pulsincap® system**

**2) Osmosis based system:-**

**a) PORT SYSTEM:-**These system consist of a gelatin capsule coated with a semi-permeable membrane (e.g.-cellulose acetate) housing an insoluble plug (lipidic) and the drug is loaded with an osmotically active agent. When it comes in contact with the aqueous medium water its diffuse out through the semi-permeable membrane, and to increased inner pressure that ejects the plug after a lag time. And the lag time is controlled the thickness of semi-permeable. Such a system was to deliver methylphenidate used in the treatment of attention deficit hyperactivity disorder as the pulsatile port system.[18,19]

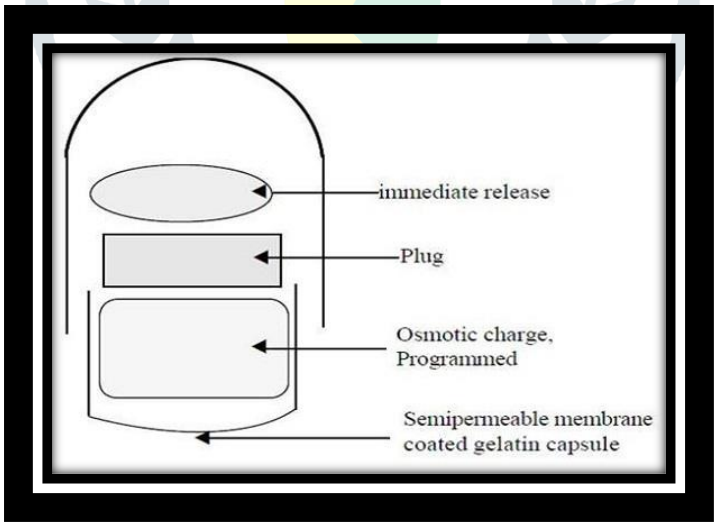


**Figure 4: Design of PORT® SYSTEM**

**3) Solubilization or erosion system: -** In these system, the core containing drug is coated with the soluble or erodible polymer as the outer layer and finally the drug release is controlled by the dissolution or erosion of the outer layer. The release of the active ingredient can be controlled by thickness and viscosity of the each coat.

- **"TIME CLOCK SYSTEM":-**It consist of a solid dosage form with lipid barrier containing carnauba wax and bees wax along with surfactants, such as polyethylene sorbitan monoleate.
- The major advantage of such system it is ease of manufacture without the need of any special equipment. The disadvantage of such system is premature drug is release when the penetrating water dissolve to the drug.
- **"CHRONOTROPIC SYSTEM":-** It consist of a core containing drug reservoir coated with hydrophobic polymer(like HPMC).These system is composed of a drug containing core and swells polymeric coating of HPMC to show slow interaction with aqueous fluids 4,8,9,11,13,14,15,16,17.The system is suitable for tablets and capsule formulation.[20,21]

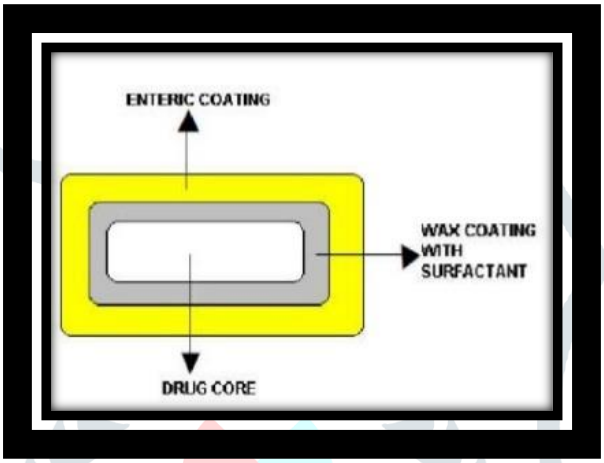


**Figure 5:Design of TIME CLOCK SYSTEM**

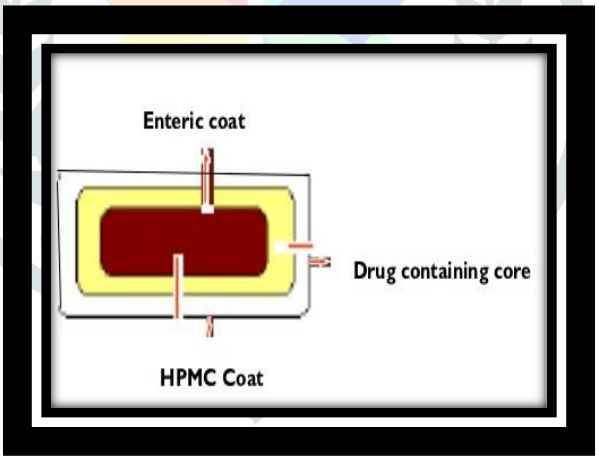


**Figure 6: Design of CHRONOTROPIC SYSTEM**

**4) System with rupturable coating membrane:-**These system based upon a reservoir system is coated with a rupturable membrane. The system are dependent on the disintegrating of the coating for the release of drug. The pressure is necessary for the rupture coating can be achieved by the effervescent excipient, swelling, disintegrants or osmotic pressure. A mixture of sodium bicarbonate or citric acid was loaded in a tablet core coated with ethyl cellulose and the $CO_2$ developed after penetration of water into the core resulted in a pulsatile release of drug after rupture. And the release may depend on mechanical resistance of the outer membrane.

- Tablet of buflomedil HCL prepared by direct compression. It is used in the treatment of peripheral arterial disease.[22]

**B) Multiple Unit based system:-**

**1) Rupturable coating based system:** It is a time-controlled explosion system. This type of system is a multiple based system in which the drug is loaded on non-pareil sugar seeds followed by a swellable layer and an insoluble top layer and the used of swelling agent include superdisintegrant like sodium carboxymethyl cellulose, L-hydroxypropyl cellulose. The used of coating polymer like polyvinyl acetate, polyethylene glycol etc. An effervescent system comprising a mixture of tartaric acid and sodium bicarbonate can be used. It is comes in contact with water, the swellable layer expands, resulting in rupture of coat film with subsequent rapid drug release.

- The release of drug is independent of environment factor like drug stability and pH.The lag time depend on thickness and amounts and type of plasticizer are used in the outer most layer. A rapid release of drug after the lag phase was achieved with increased the concentration of osmotic agent. In vivo studies of time controlled explosion system(TCES) with an in –vitro lag time of 3 hours to showed appearance of drug in blood after 3 hours, and maximum blood level is achieved after 5 hours.[23,24,25]

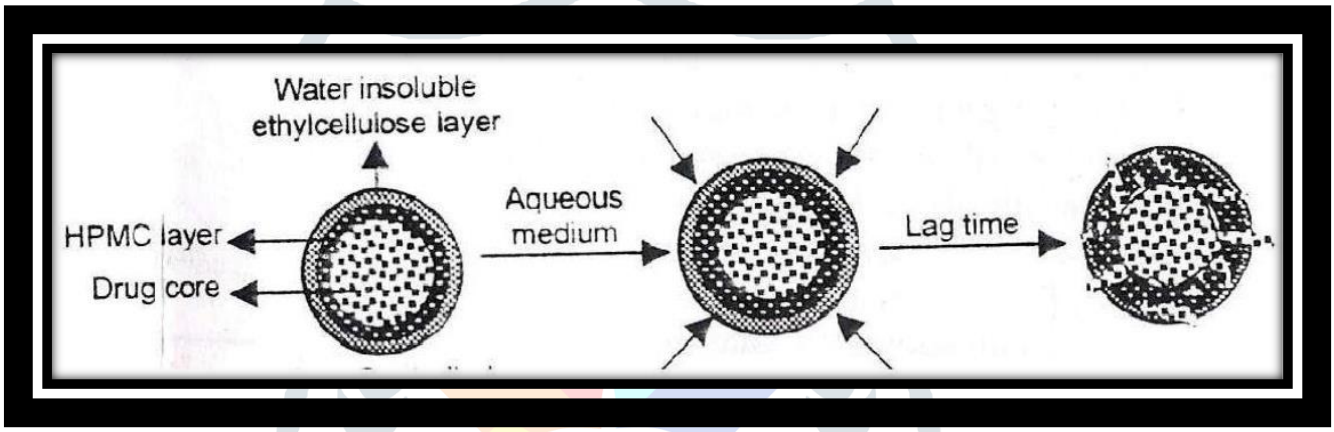


**Figure 7: Design of time explosion system**

**2) Osmotic based rupturable coating system: -** It is permeability controlled system .This system is based on a combination of osmotic and swelling effect. The core containing the drug and the low density of solid and or/liquid lipid material (e.g. Mineral oil) and a disintergrant was prepared. This core is coated with a cellulose acetate .Upon immersion in aqueous medium, water is penetrates to the core displacing lipid material. After depletion of lipid material, internal pressure is increase until a critical stress is reached, resulting in rupture of coating.

- Another system is based upon the capsule or tablet.It is composed of a large number of pellets of different release pattern. Each pellets consisting of two or more pellets or parts(e.g. population).Each pellets has a core that contain the therapeutic drug or a water soluble osmotic agent coated with water permeable, water insoluble polymer film. A hydrophobic, water soluble agents that after permeability (e.g.-fatty acid, wax or a salt of fatty acid) is loaded into the polymer film. The rate of water influx and drug efflux causes the film coating of each formulation is differ from any other pellets coating in the dosage form.
- And osmotic agent is dissolve in the water causing the pellets to swell, thereby regulating the rate of drug diffusion. The effect of each pellets formulation releasing its drug content sequentially to provides a series of pulses of drug from a single point. The thickness of coating can be varied amongst pellets. This system was used for the treatment of antihypertensive drug diltiazem.The pellet cores consisted of drug and sodium chloride were coated with a semi-permeable cellulose acetate polymer. This polymer is permeable to water and is impermeable to the drug. The lag time is increase the

thickness of coating and higher amount of talc or lipophilic plasticizer in the coating. The sodium chloride facilitated the desired fast release of drug.

3) **Pulsatile delivery system by changes in membrane permeability:**-A Sigmoidal release system (SRS) is reported which is based upon the interaction of acrylic polymer with quaternary ammonium group in the presence of counter ions. It consist of pellets cores containing drug and succinic acid coated with ammoniomethylate polymer USP/NF type B.The water influx through permeable membrane determine the lag time. The water is dissolve in acid and the drug in the core. The acid solution is turn to increase permeability of the hydrated polymer film. This system was tested in beagle dogs.

- Several delivery system based on the ion exchange have been developed.Eudragit RS 30 D is developed to be polymer o choice for the purpose.[26]

## II) STIMULI INDUCED SYSTEM:-

**A) Temperature induced system:**-This deviation sometimes can act a stimulus that triggers and the release of therapeutic agent from several temperature responsive drug delivery system for diseases.

- These system induced triggered drug delivery system utilize various polymer properities,including the thermally reversible coil/globule transition of polymer molecules swelling change of networks, crystalline melting and glass transition.

1) **Thermoreponsive hydrogel system:-** These system have been developed for chronomodulated drug release. It undergoes hydrogel employ to which reversible volumes changes in response to change in temperature known as thermo sensitive gel. These gels shrink a transition temperature it is referred to the lower critical solution temperature (LCST) of the liner polymer.

- It is sensitive hydrogels have a certain chemical attraction for water, and therefore it absorb water and swell at temperature below the transition temperature whereas they shrink or deswells at temperature above the transition temperature by expelling water.
- The most common characteristics of the temperature sensitive polymer is the presence of hydrophobic groups, such as methyl, ethyl and propyl group.[27,28,29]

**B) Chemical stimuli induced system: -** These system release of drug after stimulation by any biological factor like enzyme, pH or any other chemical stimuli. The most prominent application for this system has been development of a system that can automatically release insulin in response to elevated blood glucose level. The example of chemical stimuli induced are PULSINCAP®TM and PORT®system.

**1) pH sensitive drug delivery system:-**It contain two components one is of immediate release and other one is pulsed release and the release of 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 gastrointestinal tract pH dependent polymer is selecting for drug release at specific location can be obtained.
- Example of pH dependent polymer induce cellulose acetate phtehalate,polyacrylate,sodium carboxymethylcellulose.These polymer also used as enteric coating material so as to provide release of drug in the small intenstine.Eg-Eudragit in colon targeted system.

**2) Glucose response insulin release device:-**In these device insulin is release on increasing of blood glucose level. In case of diabetes mellitus there is rhythmic increase in the level of the insulin at proper time.

- In a glucose rich environment such as the blood-stream after a meal, the oxidation of glucose to gluconic acid catalyzed by glucose oxidase can lower the pH to approximately 5-8.This pH change induces swelling of the polymer which results in insulin release. Insulin by virtue of its action reduces blood glucose consequently gluconic acid level also gets decreased and system turns to the deswelling mode there by decreasing the insulin release.
- Example of the pH sensitive polymer include N, N-dimethyl amine ethyl methacrylate, chitosan, polyoletc.

**3) Inflammation induced system: -** 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 the inflammation responsive cells.

- Degradation via hydroxyl radical however, is usually dominant and rapid when hyaluronic acid gel is injected at inflammatory sites.
- It is possible to treat patient with inflammatory disease like rheumatoid arthritis; using anti-inflammatory drug incorporated HA gel as new implantable drug delivery system.

**4) Enzymatically Activated liposomes:-**In these system drug is loaded in liposomes was incorporate into microcapsules were coated with phospholipase A2 to achieve pulsatile release of drug molecule.

- Phospholipase A2 was shown to accumulate at the water/liposome interfaces and remove an acyl group from the phospholipids in the liposomes.
- Destabilized liposomes release their drug molecules thus allowing drug release to be regulated by the rate determining microcapsule membrane.[30-34]

## III.EXTERNALLY REGULATED PULSTILE DRUG DELIVERY SYSTEM:-

In these system release of drug in a pulsatile manner. These system is not self-operated, but instead require externally generated environmental changes to initiate drug delivery. It can include magnetic field, ultrasound, electric field, light and mechanical force.

**A) Magnetically induced system:-**It contain magnetic beads in the implant. On application of the magnetic field, drug release occurs b/w of magnetic beads. Development of different formulations for in vitro magnetically triggered delivery of insulin beads on alginate spheres.

- Magnetic carrier receive their magnetic response to a magnetic field from incorporated materials such as Magnetite, Iron, Nickel, Cobalt etc. For biomedical applications, magnetic carriers must be water – based, biocompatible, non-toxic and non-immunogenic mechanistic approach based on magnetic attractions the slowing down of oral drug in the gastrointestinal system.

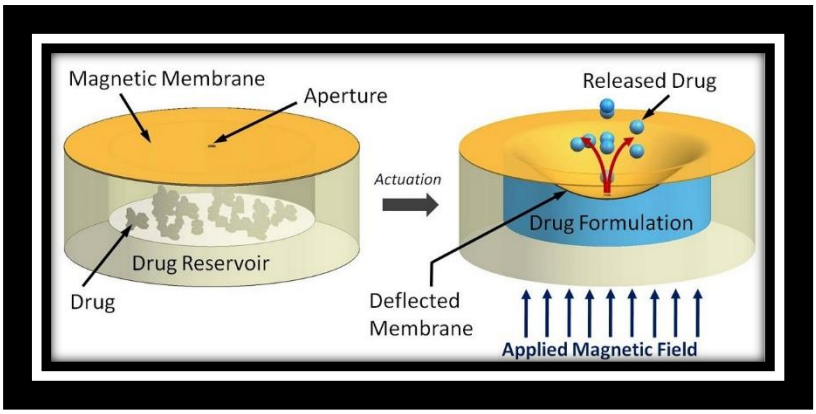


**Figure 8: Magnetic induced system**

**B) Electrically induced system:-**Electrically responsive delivery systems are prepared from polyelectrolytes (polymer which contain relatively high concentration of ionisable groups along the backbone chain) and are thus, pH-responsive as well as electro-responsive.

- Under the influence of electric field, electro responsive hydrogels generally bend, depending on the shape of the gel which lies parallel to the electrodes whereas deswelling occurs when the hydrogel lies perpendicular to the electrodes.
- E.g.: poly (acrylamide-grafted-xanthan gum) hydrogel for transdermal delivery of ketoprofen.

**C) Ultrasonically induced system**: - In these system ultrasound is mostly used as an enhancer for the improvement of drug permeation through biological barriers, such as skin.

- Ultrasound devices are used to achieve up to a 27-fold increase in the release of 5-fluorouracil from an ethylene and vinyl acetate matrix.
- Increasing the strength of the ultrasound resulted in a proportional increase in the amount of 5-fluorouracil released.

**D) Photo induced system:-**The interaction between light and material can be used to modulate drug delivery. Light-sensitive hydrogels have potential applications in developing optical switches, display units, and ophthalmic drug delivery devices.

- When hydrogel absorb the light and convert it to heat, raising the temperature of composite hydrogel above its LCST, hydrogel collapses and result in an increased rate of release of soluble drug held within the matrix.[35-39]

## RECENT ADVANCES IN CHRONOMODULATED DRUG DELIVERY:-[40-45]

Currently pharmaceutical company focused on developing and commercializing pulsatile drug product that fulfill medical needs for the treatment of various disease(e.g.:bronchial asthma,hypertension,myocardial infarction etc.) influenced by circadian rhythms, delayed or in this review are-

**1) Pulsincap™Technology:-**It was developed by R.R Scherer International Corporation. This device consists of a non-disintegrating half capsule body. A water impermeable capsule body with hydrogel plug. Plug length and insertion depth control lag time.

**2) Orbexa®Technology:-**It was developed by Aptalis Pharmaceutical Technologies. This technology is a multiparticulate system that enables high drug loading and it is suitable for product that require granulation.

**3) DIFFUCAPS®Technology:-**It is multiparticulate bead system comprised of multiple layers of drug, excipients and release controlling polymer. This technology is especially suitable for drug that traditionally require multiple daily doses needing customized release formulation

**4) DIFFUTAB Technology:-**This technology enables customized release profile and region specific delivery.Diffutab is particularly useful for high dose product and drugs that require sustained release and or once a day dosing.

**5) SODAS®Technology :-(Spheroidal Oral Drug product Absorption System)** it is based on the production of controlled release beads. It is characterized by its inherent flexibility, enabling the production of dosage forms.

**6) PRODAS®Techonology :-(Programmable Oral Drug Absorption System)** it is a multiparticulate technology, which is unique in that it combines the benefits of tableting technology within a capsule. This technology can be used to pre-program the rate of drug release.PRODAS ®Technology, by is incorporating minitablets with different release rates.

**7) CONTIN®Technology**:-It was developed by Purdue Pharma.It provides for closer control over s tablet forms for aminophylline,theophylline,morphine and other drugs .This technology has sufficient control over drug release to the blood and reduces the chances of unwanted side effects.

**8)Codas®(Chronotherapeutic Oral Drug Absorption System**):-It was developed by Elan Corporation USA.CODAS®Technology to achieve this prolonged interval.Verelan®PM uses for bedtime dosing,incorportating a 4 to 5 delay in drug delivery result in a maximum plasma concentration of verapamil in the morning hours.

**9) Egalet®Technology:-**It was by Denmark. Time of release cannbe modulated by the length and composition of plugs. Several opioid products are developed using this technology.

**10) IPDAS® (Intestinal protective drug absorption system):-**It is a new oral drug delivery approach that is applicable to gastrointestinal (GI) irritant drug (NSAIDS) class.IPDAS®was initially designed as part of the development process for Elan Drug Technologies 'proprietary naproxen formulation.

**11) GEOCLOCK®Technology:-**It was developed by SkyePharma.It is in form of chronotherapy focused press-coated tablets. It is a novel technology to develop Lodotra™, a rheumatoid arthritis drug.

**12) Geomatrix®Technology:-**It was developed by Skype Pharma Plc. USA.Some of the drugs that are marketed based on this technology are Diltiazem hydrochloride, Nifedipine,and Diclofenac Sodium.

**13) Pulsys™Technology:-**It was developed by Middle Brook Pharmaceuticals. This technology was used to develop chronotherepeutic system for amoxicillin.PULSYS Technology's Moxatag therapy in once daily formulation.

**14) Minitabs®:-** Eurad's Minitabs is tiny (2mm*2mm) cylindrical tablets coated with a functional membrane to control the rate of drug release. It is also used as sprinkle on food. It can be used as a sprinkle on food. It can also be used as sprinkle for pediatric and geriatric patients who have difficulty swallowing tablets.

**15) ACCU-T CR Tri layer tablets:-**It applies controlled release technology to further enhance treatment options. It provides a solution to this problem and introduces dose flexibility into CR dosage form.

**16) Banner's Versertol Technology:-**It is a novel innovative technology that provides time controlled release for wide range of drug. This technology is versatile because depending on physiochemical properties of drug either emulsion or suspension.

**17)The Ceform™ Technology:-**Ceform®Technology is based on "melt-spinning", which means subjecting solid feedstock (i.e., combination of bioactive agent/biodegradable polymer) to a combination of mechanical forces,temperature,thermal gradient and flow rate during processing.

**18) Chronotropic®Technology:-**In this technology containing core is coated with an outer release controlling layer. Both single and multiple unit dosage form such as tablets and capsules, minitablets, pellets have been employed as the inner drug formulation.

**19) Covera-HS:-**Covera-HS is the first formulation of an antihypertensive/antianginal agent. It is an novel drug delivery system to mimic the body's typical 24 h circadian variations in blood pressure and heart rate.COER-24 TM (Controlled onset extended release) is a unique delivery technology was developed in conjunction with AlzaCorp.Covera-HS is the only controlled release verapamil formulation that is currently approved for the management of both hypertension and angina pectoris. It is designed for oral dosing at bedtime.

**20) Oros® Technology:-Chronset™** is a proprietary OROS delivery system that delivers a bolus drug dose in a time or site-specific manner to the gastrointestinal tract. This system is based on osmosis. It is generally used for designing of extended release tablet.

**21) Magnetic nano composite hydrogen:-**It is temperature responsive hydrogel was used as a controlled pulsatile drug delivery.

**22) Microfabrication:-**The release mechanism is based on the electrochemical dissolution of thin anode membranes covering micro reservoirs filled with chemicals in solid, liquid or gel film.

**23)Timer® Technology:-**This technology is based on hydrogel controlled release device. It can provide from zero order to chronotherapeutic release. It can also provide different release kinetic interaction.

**24) DMDS Technology:-DMDS (Dividable Multiple Action Delivery System)** is developed to provide greater dosing flexibility that improve product efficacy and reduces chances of side effect.

**25) Three-Dimensional printing®(3DP) Technology:-** It is a novel technique based on solid freedom fabrication method. Different type of complex for oral drug delivery device such as pulse release,immediate release, breakaway tablet and dual pulsatory tablet developed by using the 3DP process.

## CURRENT AND FUTURE DEVELOPMENT:-

Over the last decades there has been a growing appreciation on the importance of circadian rhythm on GI physiology and on disease states, together with the realization of the significance of the drug administration on resultant pharmacodynamics and pharmacokinetic parameters.

The future of drug delivery system as pulsatile manner seems to be very promising for certain disease. It provides maximum advantages over the zero or first order drug delivery mechanism. Various system has to be developed like site specific, time controlled, single or multiple unit are obtained by chronomodulated drug delivery technique.

Many more disease could be studies for their chrono-behaviour .There exists a definite need in future to identify and formulate many more drugs by pulsincap techonology for their chronomodulated drug delivery for a effective treatment.[46]

## MARKETED PRODUCT OF CDDS:-[47-52]

**Table 2: Marketed product of CDDS**

| S.NO | TECHOLOGY | API | DISEASE |
|---|---|---|---|
| **1.** | **DIFFUCAPS®** | Propranolol HCL,Verapamil HCL | Hypertension |
| **2.** | **CEFORM®** | Diltiazem HCL,Verapamil HCL | Hypertension |
| **3.** | **OROS®** | Methylphenidate HCL | Anti-psychotic |
| **4.** | **Pulsincap™** | Dofetilide | Hypertension |
| **5.** | **Pulsys®** | Amoxicillin | Pharytisgitis |
| **6.** | **Uniphyt®** | Theophylline | Asthma |
| **7.** | **CONTIN®** | Theophylline | Asthma |
| **8.** | **Three-dimensional printing®** | Diclofenac sodium | Inflammation |
| **9.** | **TIMERX®** | Oxymorphone | Pain management |
| **10.** | **OROS ®** | Paliperidone | Schizophrenia |
| **11.** | **PROCARDIA XL®** | Nifedipine | Hypertension |
| **12.** | **Physio-chemical modification of API** | Simvastatin | Hypercholesterolemia |

**CONCLUSION:-**

Targeting the drug at specific site of the GIT to determine time based release of drug which helps in chronotherapy.Many disease can show severity at particular time intervals, called chronodiseases (like hypertension,asthma,arthritis,cardiac attack etc) which generally maximizes at early mornings, thus requiring to modulate the drug level in synchrony with circadian rhythms of the disease.Hence,this novel pulsincap technique helps in delivering and maintaining the drug level in synchrony with the circadian rhythm of the disease.

It can concluded that chronomodulated drug delivery system offers a solution for delivery of drugs exhibiting chronopharmacological behavior, extensive first pass metabolism, necessity of night –time dosing, or absorption window in GIT.These system shall be promising in future because delivery of drug in this system when its actual concentration is needed as per chronological need.[46]

## REFERENCES:-

1. Neeraj Singh ,Nisha, Vivek Gill,Parina Gill, Sukhbir Singh "Chronopharmceutical Drug Delivery System: A Guided Therapy" International Research Journal of Pharmaceutical and Applied Sciences 2013;3(4);84-87.

2. Patel Vipul P, Soniwala Moinuddin M "Pulsatile Drug Delivery System for Treatment of Various Inflammatory Disorder: A Review" International Journal of Drug Development and Research, July-Sept-2012; Vol. 4; 67-87.

3. Susan Schmidt. Biocompatibility of silicon based electrode arrays implanted in feline cortical tissue. J. of Biomedical materials research.1993; 27(11): 1393-1399.

4. M. Hu, T. Discrete chemical release from a microfluidic chip. J. Microelectromech. Syst. 2007; 16(4): 786–794.

5. Harkness JAL, Richter MB, Panayi GS. Circadian variation in disease activity in rheumatoid arthritis. British Medical J.1982; 284: 551-55.

6. Huskisson EC and GP Velo ed. Chronopharmacology of anti-rheumatic drugs with special reference to indomethacin in: Inflammatory Arthropathies. Excepta Medica. 1976: 99-105.

7. Bellamy N, Sothern RB, Campbell J. Rhythmic variations in pain perception in osteoarthritis of the knee. Journal of Rheumatology.1990; 17: 364-372

8. K. Moin, Vishnu P. Pulsatile Drug Delivery System for Colon –A Review. International journal of research in pharmaceutical and biomedical sciences. 2011; 2(3):934-41.

9. Gopi V. New Tool for Timed, Pulsatile Drug Delivery. Pharmaceutical formulation and quality. 2005.

10. D. Hitesh, Jayvadan P. Chronpharmaceutics, pulsatile drug delivery system as current trend. Asian journal of pharmaceutical sciences 2010; 5(5):207-30.

11. A. Alexander, N. Bhoyar, M. Sharma, et al. Important Aspects and Fundamentals of Chronotherapeutic Drug Delivery System for Optimizing Therapeutic Effect. A Review. American Journal of PharmTech Research. 2012; 2(2):755-91.

12. G.RASVE, G. BORADE, S. DESHMUKH, et al. PULSATILE DRUG DELIVERY SYSTEM: CURRENT SCENARIO. International journal of pharma and bio science. 2011; 2(3). Epub 332.

13. Reinberg A, Manfredi R, Kahn MF. Tenoxicam chronotherapy of rheumatic diseases. Annual Review of Chronopharmacology. 1990; 7: 293-296.

14. Sharma S, Pawar SA. Low density multiparticulate system for pulsatile release of meloxicam. Int J Pharm. 2006; 313: 150-158.

15. N. Kanaka Durga Devi*, B.Sai Mrudula, A.Prameela Rani; "Chronomodulated drug delivery system of Montelukast sodium" Scholars Research Library 2010, 2(5): 316-329.

16. Wilding IR, Davis SS, Bakhshaee M et al. Pharm Res, 1992; 9: 654-657.

17. Stevens HNE et al. Evaluation of Pulsincap™ to provide regional delivery of dofetilide to the human GI tract. International journal of pharmaceutics, 2002; 236 (1): 27-34.

18. Amidon GL, Leesman GD. Pulsatile drug delivery system. Google Patents; 1993.

19. Balaban SM, Pike JB, Smith JP, Baile CA. Delivery devices with pulsatile effect. Google Patents; 1994.15. Tangri P, Khur

20. Gazzaniga A, Iamartino P, Maffione G, Sangalli ME. Oral delayed-release system for colonic specific delivery. International Journal of Pharmaceutics. 1994; 108(1):77-83.

21.Maroni A, Sangalli M, Cerea M, Busetti C, Giordano F, Gazzaniga A. Low viscosity HPMC coating of soft and hard gelatin capsules for delayed and colonic release: preliminary investigations on process parameters and in vitro release performances. Proceedings of the Controlled Release Society. 1999; 26(26):885-6.

22. Sharma G S, Srikanth MV, Uhumwangho MU, Phani Kumar K S et al, "Recent Trends in Pulsatile Drug Delivery Systems", Int. J. Pharm. 2010; 2: 201-208.

23. Beckert TE, Pogarell K, Hack I, Petereit H-U. Pulsed drug release with film coatings of Eudragit & Mac226; RS 30D. Proceed Int'l Symp Control Rel Bioact Mater. 1999; 26: 533-534.

24. Guo X. Physicochemical and Mechanical Properties Influencing the Drug Release from Coated Dosage Forms. Doctoral Thesis. The University of Texas at Austin; 1996.

25.Narisawa S, Nagata M, Danyoshi C, Yoshino H, Murata K, Hirakawa Y, Noda K. An organic acid-induced sigmoidal release system for oral controlled-release preparations. Pharm Res. 1994; 11(1): 111-116.

26. Guo, X. PhD thesis, The University of Texas, Austin, 1996.

27. Okano T et al. Advances in Polymeric Systems for Drug Delivery, Gordon and Breach, Yverdon, Switzerland, 1994.

28. Bae YH et al. On–off thermocontrol of solute transport. I. Temperature dependence of swelling of N-isopropylacrylamide networks modified with hydrophobic components in water. Pharm Res 1991; 8 (4): 531–537.

29. Kim SW et al. On–off thermocontrol of solute transport. II. Solute release from thermosensitive hydrogels. Pharm Res 1991; 8 (5): 624–628

30.Kataoka K et al. Nagasaki. Block copolymer micelles for drug delivery: design, characterization and biological significance. Adv. Drug Deliv Rev 2001; 47: 113–131.

31. shihara K et al. Control of insulin permeation through a polymer membrane with responsive function for glucose, Makromol. Chem Rapid Commun 1983; 4: 327–331.

32. Berner B, Dinh SM. Electronically assisted drug delivery: an overview. Electronically Controlled Drug Delivery 1998: 3–7.

33.Kishi R, Hara M, Sawahata K, Osada Y. Conversion of chemical into mechanical energy by synthetic polymer gels (chemomechanical system). Polymer Gels —Fundamentals and Biome
dical Applications, Plenum Press: New York, 1991; pp. 205–220.

34. Kwon IC et al. Stimuli sensitive polymers for drug delivery systems. Makro mol Chem Macromol Symp 1990; 33: 265–277.

35. Santini JT, Cima MJ. A controlled release microchip. Nature 1999; 335-38.

36. Santini JT et al. Microchips as controlled-drug delivery devices. Angew Chem Int Ed 2000; 2396-2407.

37. Saslawski O, Weigarten C. Magnetically responsive microspheres for the pulsed delivery of insulin. Life Sci 1988; 42 (16): 1521-1528.

38. Bae YH, Okano T. A reversible antigen-responsive hydrogel. MakromolChem1987; 8: 481-485.

39. Edukondalu V et al. An Overview on Pulsatile Drug Delivery System. PharmaTutor 2013; 1(2):17-22

40. MacNeil ME, Rashid A, Stevens HN. Dispensing device. World Patent 1990; 9009168.

41. Stevens HNE, Wilson CG, Welling PG, et al. Evaluation of pulsincap to provide regional delivery of dofetilide to the human G.I. tract. Int. J. pharm 2002; 236:27-34.

42. Ravula AN, Goud BA, "Recent Advances in Oral Pulsatile Drug Delivery" Journal of Advanced Pharmaceutical Sciences 2011; 1:57-62

43. B.C.Youan, "Overview of chronopharmaceutics, in: B.C. Youan (Ed.), Chronopharmaceutics: Science and Technology for Biological Rhythm Guided Therapy and Prevention Diseases", John Wiley & Sons, Inc, 2009.

44. Verma RK and Sanjay G. Current Status of Drug Delivery Technologies and Future Directions. Pharmaceutical Technology On-Line. 2001; 25(2):1-14.

45. Roy P and Shahiwala A. Multiparticulate formulation approach to Pulsatile Drug delivery: Current perspectives. Journal of Controlled Release. 2009; 134:74– 80.

46. Balfour JA, Fitton A, Barradell LB. (2004), "Lornoxicam. A review of its pharmacology and therapeutic potential in the management of painful and inflammatory conditions", Adis International Limited, Auckland, New Zealand.

47. Prasanth V.V, Modi Mitesh P., and Mathew Sam T: Pulsatile: A tool for circadian rhythm –a review. Journal of Drug Delivery & Therapeutics 2012; 2(1): 58-65.

48. Sharma Ritika, Singh Arjun, Kumar Sunil, Jamil Faraz: Pulsatile drug delivery system. International Research Journal of Pharmacy 2012; 3(7): 103-107.

50. Patel JD, Aneja K, Majumdar S H, "Pulsatile Drug Delivery System: A "User Friendly" Dosage Form" JPRHC 2010; 2: 204-215.

51.Sharma G S, Srikanth MV, Uhumwangho MU, Phani Kumar K S et al, "Recent Trends in Pulsatile Drug Delivery Systems", Int. J. Pharm. 2010; 2: 201-208.

52.Rasve G, Borade G, Deshmukh S, Tagalpallewar A, "Pulsatile Drug Delivery System: Current Scenario", International Journal of Pharma and Bio Sciences 2011; 2: 332-343.