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ADVANCED DRUG DELIVERY IN DESIGNING OF BIOLOGICAL RHYTHM THROUGH PULSATILE DRUG DELIVERY SYSTEM: TECHNOLOGY AND CHRONOPHARMACOLOGICAL BEHAVIOUR

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ABSTRACT

Pulsatile drug delivery system has opened up new challenges in the field of delivering a drug at the exact position at the exact time and the exact quantity , which provides more benefit then conventional doses form . These system are intended to meet body's biological rhythm and deliver according to circadian behavior of disease. The drug is released fastly and totally as a pulse after a lag time has to be design in such a way that total and fast drug release should follow the lag time such system are also called time controlled as a drug release is self-regulating of the environment.

Circadian rhythm plays a major role in the regulation of metabolism , physiology, behaviour, sleep pattern, insomnia, depression, and most of the body functions display circadian rhythm Example- heart rate, blood pressure, blood flow , body temperature and pH. Pulsatile drug delivery system delivers specific time for pathophysiological need of diseases and improving patient's compliance. Pulsatile drug delivery systems is important not only for drug delivery but also for diseases like cardiovascular diseases, asthma, gastric ulcer, and hypercholesterolemia . The main reason for the using pulsatile drug release is when the continous drug release is not required. This review paper presents the alteration of circadian rhythm with diseases and novel technologies involved in the manufacturing of pulsatile drug delivery system.

Key words: PDDS, Chronocopharmatherapy, Chronobiology,Mareketed technology ,

Introduction :

Day to day rhythms in living being has been found since early times. As early as the fourth century B.C., Alexander the great's scribe Androsthenes noted that the leaves of some tree opened in the day time and closed at night time present a type of rhythmecity. In 1729, the French astronomer named Jean Jacques d,Ortous deMairan carried the first experience on biological rhythm. The circadian rhythms of quality of mammalians are experienced to be robust and precise. Further in study aiming for fundamental rational to contribute both commercial and therapeutic value to product are leading to advance drug delivery phenomenon. Furthermore, Oral doses forms are must be known to provide zero order or first order release in which the drugs release at a substantially steady rate of release per unit of time. However there are immediate where maintaining a constant blood level of a drug is not a desirable. Oral controlled release drug delivery systems are designed to meet the drugs at controlled and predetermined rate thus maintaining their therapeutically effective concentration in

systemic circulation for prolonged periods. The new advancement of the technology in pharmaceutical field, over the last few decades has seen an increase in use new technique in drug delivery system.

Traditionally, drug delivery system has meant for receiving a drug with chemical engaged predictable form the intestine or form the site of injection but nowadays concept of Chronopharmaceutics has emerged wherein research is devoted to the design and evaluation of drug delivery system that release a therapeutic agent at a rhythm that ideally match the biological requirement of the disease. disease where a constant drug level are not preferred but need a pulse for therapeutic concentrate in programmed manner act as push for the development of Pulsatile delivery system. It is programmed drug release. In these methods programmed drug release i.e. pulse pattern are followed. On the other hand for certain therapy a Pulsatile drug release pattern, providing special and temporal delivery and also increase patient interest, where the drug is released after well-defined lag time, exhibits major advantages. There is a well recognized association that most of the body functions display circadian rhythms. Example; Heart rate, stroke volume, blood pressure, blood flow, body temperature and gastric pH. Further, organs and their functions vary with the time of the day. It is gradually more recognized that there are Rhythmic and temporal patterns in the symptom of many diseases state. The symptoms for a number of diseases such as bronchial asthma, myocardial infarction, angina pectoris, hypertension, rheumatic diseases, etc. follow a circadian rhythm.

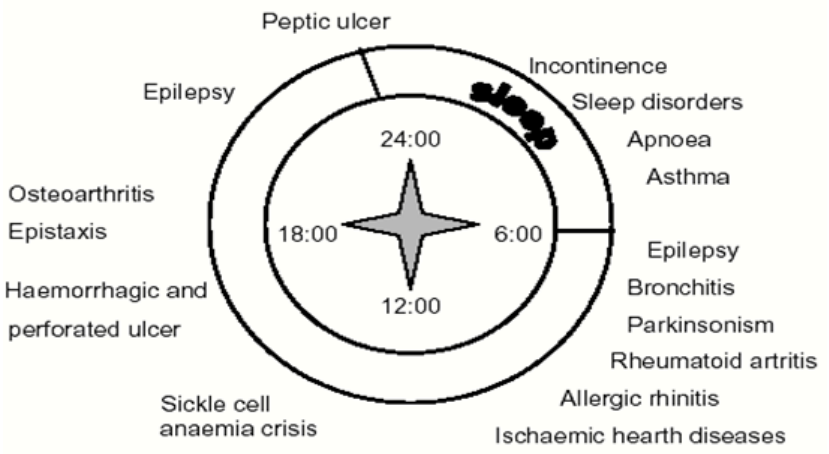
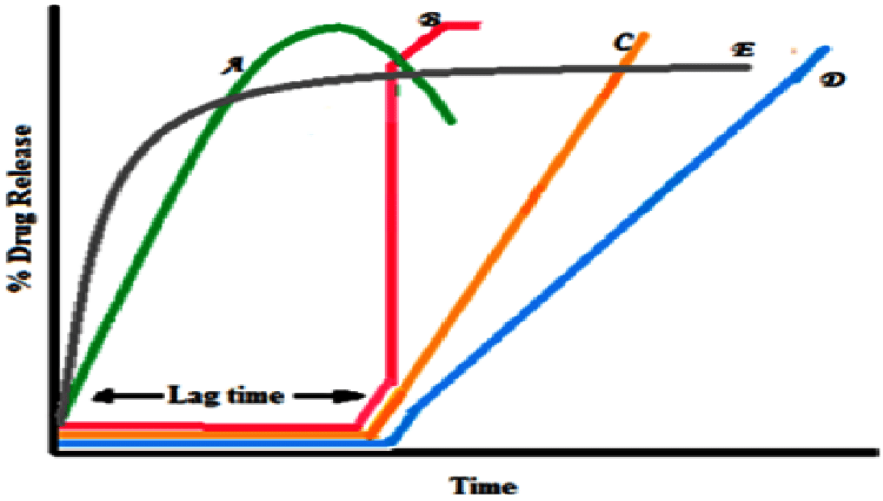


Figure – Human Circadian time structure

Circadian rhythms are self-sustaining, natural, endogenous oscillations that occur with a regular recurrence of about 24 hours. The term circadian is came from the Latin circa- which means ‘about’ and dies mean a ‘day’. Normally circadian rhythms are synchronized according to internal biologic clocks related to the sleep wake cycle and repeat on each rotation of the earth roughly every 24 hour. Although our circadian rhythm is based on sleep activity cycle and is influenced by our genetic make-up and thus affects our body’s functions during day and night.



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Drug release from PDDS Where, A: conventional release profile, B: Burst release of drug as a after a lag time, C: Delayed release profile after a lag time, D: Constant release profile in prolonged period after a lag time, E: Extended release profile without lag time.

Merit;

a. Decreases side effects and no risk of dose dumping.
b. Reduce in dose frequency.
c. Improve stability in GIT.
d. Less inter and intra subject variability.
e. Nearly constant drug level at the site of action.
f. Extended daytime or night time activity.
g. Protection of the mucosa from irritation from certain drug.
h. Drug loss is prevented by extensive first pass metabolism
i. Reduced dose of drug without decrease in therapeutic effect.
j. Improve patient compliance.
k. The system can be utilized for many solid dosage form like granule, microspheres , microparticle, tablet ,capsule and pellets
l. Increase absorption and bioavailability the conventional immediate release and sustain released drug
m. Decrease effect of food(change occurring in bioavailability of drug when given with food)
n. Drug release is not affected by change in pH of GIT
o. API that attains biological tolerance demand for a phenomenon that will exclude their continous presence at the biophase as this run to cut down their beneficial outcome.

Demerit;-

a. Floating system is not possible for that type of drug that have solubility or stability problem in GIT.
b. These system have need of a high level of fluid in the stomach for drug delivery to float over a stomach
c. Lack of manufacturing reproducibility and efficacy is major problem.
d. Higher cost of production is involved.
e. Trained and skilled person needed for manufacturing of dosage form.
f. It develop a 24 hour sleep wake syndrome,
g. Person may also be underprivileged of sleep sometimes.
h. Patient need to consult the doctor regularly to avoid side effect.

Requirement Of PDDS ;

a. Chronopharmacotherapy of disease which show circadian rhythm in their pathophysiology-
   - Asthmatic attack during early morning
   - Heart attack in the middle of the night
   - Morning stiffness in arthritis
b. Avoiding the first pass metabolism eg. Protein and peptide
c. For which the tolerance is rapidly exists Eg. salbutamol sulphate, transdermal nitroglycerine
d. For targeting specific site in intestine Eg. Colon (sulphasalazine), crohn's disease and enhance deliver of protein and peptide.
e. For time programmed administration of hormone and drug
f. For drug having the short half life Eg. beta blockers
g. Body function that follow circadian rhythm
h. When rhythmic variation seen in acid secretion in stomach, gastric emptying and GIT blood transfusion
i. The lag time is necessary for the drug that go through degradation in gastric acid medium
j. Local therapeutic need – Inflammatory bowel disease

Suitable Drug For PDDS

1. Drug which are locally active in the stomach e.g. Mesoprostol, Antacid
2. Drug that can disturb normal colonic microbial flora e.g. Antibiotics that used for the eradication of H. Pylori such as Clarithromycin, Amoxicillin, Tetracyclin.
3. Drug that exhibit low solubility at high pH value e.g. Chlorodiazepoxide, Varapamil, Diazepam
4. Drug that have narrow absorption window in GIT e.g. L- Dopamine, Para amino benzoic acid, Furosemide, Riboflavin

5. Drug those are unstable in the intestine or the colonic environment e.g. Ranitidine, Captopril, Metronidazole, HCL

Mechanism of action drug release from PDDS

The mechanism of action drug release from PDDS can be occurring in the following step include bulk erosion of the polymer in which drug release by diffusion is restricted, surface erosion of layer device composed of alternating drug contain and drug free layer, osmotic controlled rupture.

1. **Diffusion-** water diffuse into the interior part of the particle when particle comes in contact with aqueous fluid in the GIT and the drug solution diffuse into across the release coat to the exterior
2. **Erosion-** These type of system generally contain reservoir device coated with a barrier layer. The barrier dissolves or erodes after a specified lag period, after which the drug is released rapidly from the reservoir core. In simple word some coating design to erode gradually with respect of time and result in the release of drug content within the particle.
3. **Osmosis-** the osmotic system consist of capsule coated with the semi porous covering . fill of the capsule was insoluble plug ,osmotically active agent and the API formulation. When the capsule comes in touch with the body fluid. The semipermeable tissue layer allow the entry of water, which induced the force to formulated and the insoluble plug bushed after a fixed time. The drug is force out of the particle into the exterior through the coating. EX.A PORT .

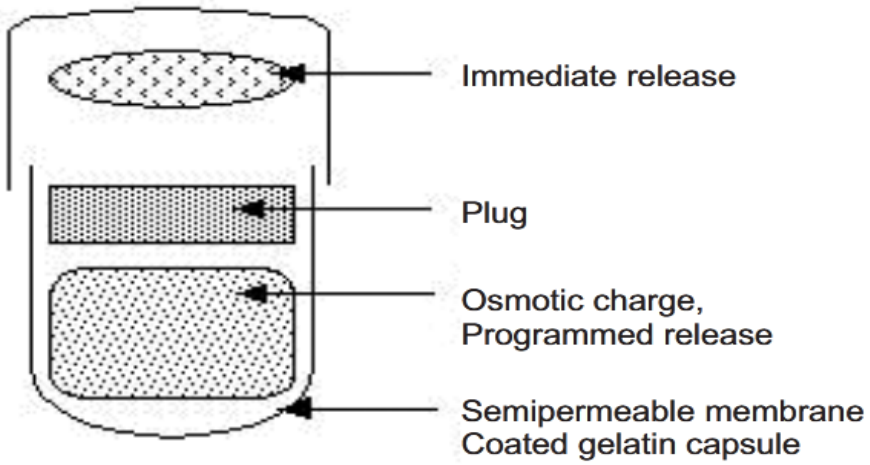


FIGURE . The Pulsatile capsule is designed for two drug doses { PORT * SYSTEM }

CHRONOCOPHARMACOTHERAPY';

The term Chronocophamacotherapy is combination of two words i.e, Chronocophamacology and pharmacotherapy. It is study of the effect of drug as a function of biological timing and characterstatic of rhythm. These rhythms are three types Circadian, Ultradian, Infradian. Chronokinetics refers to rhythmic change in bioavailability and ADME of drug. Chronocotherapy is specially relevant when the risk and strength of symptoms of a diseases a vary conventional over time. The effectiveness and toxicity of several drugs

depending on the dosing time disease with rhythmic circadian organization of the body play an important role in pharmacodynamics and pharmacodynamics of the drug is not contact within 24 hrs.

Diseases with circadian rhythms:

As many conditions show circadian pattern, advantage could be taken by timing and adjusting the administration of drugs according to the circadian rhythm of the diseases. Oral pulsatile administration could be useful for the treatment of certain diseases such asthma, hypertension gastric ulcer etc. which exhibits circadian rhythm.

Alzheimer disease

Change of circadian rhythm is studied in patient with Alzheimer's diseases had less diurnal motor activity, a higher percentage of nocturnal activity, lower interdaily stability of motor activity and a time of peak than healthy individuals. The data indicates that Alzheimer disease causes turbulence of circadian rhythms and that sundowning related to a phase delay of body temperature caused by Alzheimer's disease.[4]

Cancer

The circadian timing system control drug metabolism and cell production over the 24 hour through molecular clocks in each cell, circadian physiology and the suprachiasmatic nuclei a hypothalamic pacemaker clock that coordinates circadian rhythms. The circadian timing is tested with patients with metastatic colorectal patients. The rhythmic circadian changes in tumors blood flow and cancer growth. These are three fold greater during each daily activity phase of the circadian cycle than rest phase.

Diabetes - Insulin is released in a pulsatile passion , the basal mode of insulin secretion is subject to multitude of endogenous control system that act on the β cell both In a stimulatory eg. β agonist, glucagon and glucose and amino acid and an inhibitory fashion. Since impairment of target cell sensitivity to insulin action and hyperglycemia may be caused by the stress hormones, cortisol, epinephrine and growth hormone included with intrinsic rhythmicity.[6]

Cardiovascular Diseases

The capillary resistant and vascular reactivity is higher in the morning and decrease in the day time platelet aggregation is increased in the morning and decreased fibrinolytic activity leading to coagulation of blood.

Duodenal ulcer

Secretion of gastric acid displays circadian rhythms, gastric secretion is higher in evening in patients with duodenal ulcer and decreases in the morning .Most patients with peptic ulcers or esophageal reflux disease develop subjective symptoms of epigastralgia and retrosternal pain during the period of time from the middle of the night to the early dawn(nocturnal pain)Such pain often disappears before breakfast. Disturbed circadian rhythm of gastric acid secretion may have close relationship with the onset and aggravation of acid related diseases. [8]

Hypercholesterolemia

The diurnal variation in human cholesterol synthesis in the rapidly exchangeable pool was studied in six healthy normolipemia individuals by measurement of deuterium incorporation from body water into plasma cholesterol. The highest rate of deuteriumin corporation into free cholesterol occurred during early morning, whereas decreases the rate during afternoon and evening. This indicated circadian rhythm involves in the synthesis of cholesterol.[9]

Coagulation and thrombosis-

The interaction of the rhythms of the variables participating in hemostasis determine transient risk states of thrombo embolic events, including myocardial infarction and stroke, hemorrhage and hemorrhagic events, each with unique timing. The circadian stating of the rhythms in vascular, cellular and coagulation factors that favors blood coagulation and thrombosis coincides with the daily minimum in fibrinolytic activity; as a result there is elevated risk in the morning of acute myocardial infarction and stroke.10

Ashtma

Knowledge gained from the study of circadian alterations in physiology and inflammation need to applied clinically since the study indicated that chronotherapeutic strategies are important to the efficacious treatment of nocturnal asthma. In asthma resistant increases progressively across the night, whether subjects sleep or not, although the increase is much greater during sleep.

Circadian rhythm and manifestation of disease.

TABLE - Pathological conditions treated by Pulsatile drug delivery phenomena

S NO	Disease	Chronological behavior	Drug used
1	Peptic Ulcer	Acid secretion is high in the afternoon and night	H2 Blockers
2	Attention defect syndrome	Increasing in DOPA level in afternoon	Methyl phenidate
3	Cardiovascular diseases	BP is lower during sleep and rises at the early morning before wake up	Nitroglycerin, calcium channel blockers, ACE inhibitors
4	Asthma	Precipitation of attacks during night or at early morning	B2 agonist, antihistamines
5	Arthritis	Level of pain increases at night	NSAIDS, Glucocorticoids
6	Diabetes mellitus	Increased in the blood sugar after meal	Sulfonylurea ,Insulin
7	Hypercholesterolemia	Cholesterol synthesis is high in the night than day time	HMG COA reductase inhibitor

Chronopharmaceutical technologies -

Capsule in a capsule technology -

This technology offers a broad range of therapeutic applications. This method allows the insertion of a prefilled smaller capsule into larger, liquid filled capsule. The smaller inner capsule may contain either liquid or semi-solid formulation and according to the formulation, both capsules maybe of gelatin or HPMC composition and can be coated. Both capsules may contain the same active drug provide multiple release profiles from the dosage unit. Combination therapies are significant interest as demonstrated by the recent launches of Combodart™ (GSK) and VImovo™ (Pozen, AstraZeneca).



Figure: Capsule in capsule technology

Tablet in a tablet technology -

This technology involves the compaction of granular materials around a preformed tablet core using specially tablet equipment. Compression coated tablet has two parts, internal core and surrounding coat. The core is small porous tablet and prepared on one turret. After tablet core is manufactured it is transferred to another slightly large die that is partially filled with coating powder, more coating powder is filled on the top of the core and compressed again resulting tablet with tablet.

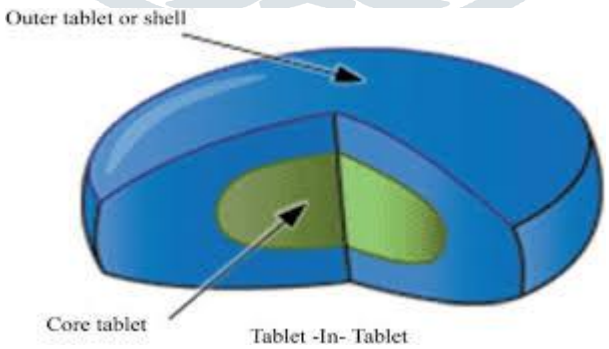


Figure : Tablet in tablet technology

Tablet in a capsule technology -

The recent approach that has come to existence is one that combines the feature of both controlled release tablet and modified release capsule in one dosage form. Drugs are encapsulated in one way or another within a barrier material, which is composed of an erodible or biodegradable polymer. After the barrier material, is dissolved eroded or degraded drugs are rapidly release from the inner reservoir core.

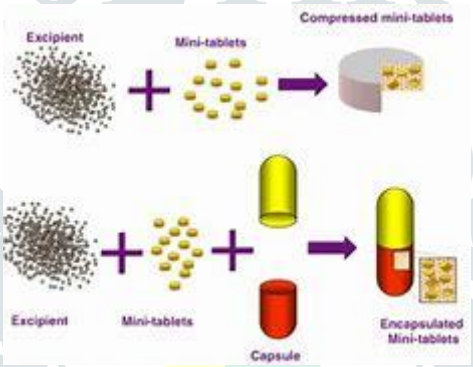
This system can be used for achieving the selective delivery of drugs at appropriate time, which is a chronopharmaceutical approach for the better treatment of diseases with circadian rhythms.



Figure:Tablets in capsule technology

Granules and tablets in a capsule technology .

Biphasic delivery systems are designed to release a drug at two different rates or at two different period of time, they are either quick/slow or slow/quick. A quick/slow release system provides an initial burst of drug release followed by a constant rate of release over a defined period of time and in slow/quick release system provides release vice versa.



Figure; Granules and tablets in capsule technology

Methodologies for Pulsatile drug delivery :

1. Time controlled Pulsatile release phenomena

In time controlled drug delivery phenomenon, Pulsatile release is received after a particular time separation in order to mimicker the circadian rhythm.

2. Stimuli induced pulsatile phenomena

In these phenomena there is release of the drug after stimulus by any biological factor like temperature,any other chemical stimuli.

3 . Externally regulated phenomena

That phenomena in which drug release is programmed by extraneous stimulation like magnetism ,ultra sound, electrical effect and erradiation.

4 . Multiparticulate / Multiple unit phenomena

These phenomena have been formulated on the basis of various approaches of designing pulsatile drug delivery phenomena discoursed before (like time controlled ,stimuli induced or outwardly influenced pulsatile drug delivery phenomena). These can be developed in various type of dosage forms like

List of marketed pulsatile drug delivery technology used

Some of the marketed drug based on PDDS technology was shown in the following table

Technology	**Mechanism**	**Proprietary name dosage form**	**API**	**Diseases**
CODAS®	Multiparticulate pH dependent system	Verelan®PM; extended release capsule	Verapamil HCl	Hypertention raised BP
OROS®	Osmotically regulated	Covera-HS*,XL tablets	Verapamil HCL	Hypertension
DIFFUCAPS*	Multiparticulate system	Innopran*;XL tablets	Verapamil HCl, Propranolol HCl	Hypertention
Pulsincap TM	Rupturable System	Pulsincap	Dofetilide	Hypertention
PULSYS	Multiparticulate system	Moxatag tablets	Amoxicillin	Tonsillitis
TIMER	Erodible/soluble barrier coating	OPANA® ER tablets	Oxymorphone	Pain management
Covera-HS	Osmotically regulated	Covera-HS ER tablets	Verapamil HCl	Hypertension
PrcardiaXL	Osmotically regulated	Prcardia XLSR	Nifedipine	High blood pressure and angina
Three dimensional printing	Externally regulated system	Their form*	Diclofenac sodium	Inflammation
CODES	pH dependent system	CODES	Anti-inflammatory	Inflammatory Colon diseases

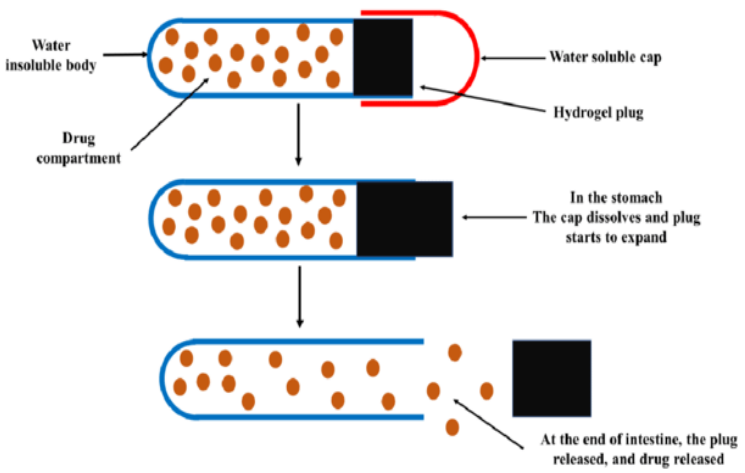


FIGURE . PULSINCAP TECHNOLOGY

Single unit phenomena is commonly intended in a capsule form.It compromise of a water insoluble capsule enclosing the drug reservoir. A swellable hydrogel plug was used to seal the drug content into the capsule body. When this capsule came contact with the dissolution fluid, it swelled, and after the lag time, the plug pushed itself outside the capsule and rapidly release the drug.API is get free for absorption. The length of the plug and its point of insertion into the capsule controlled the lag time. The polymer for hydrogel – HPMC ,PVA,PEO,PMA.

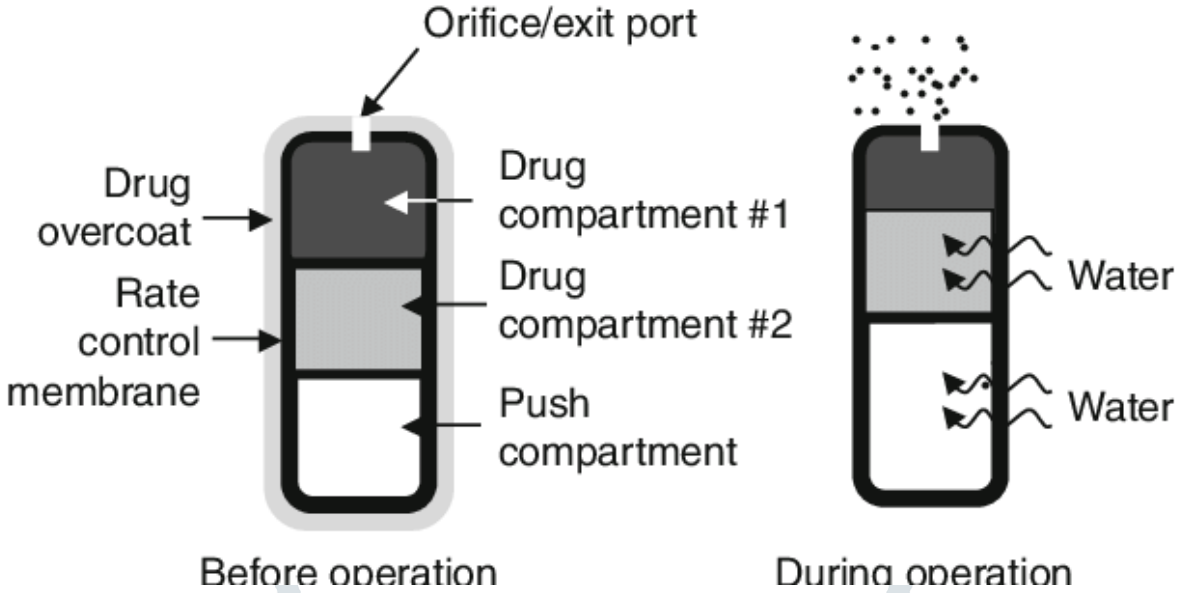


Figure. OROS technology for drug design (ALZA CORPORATION)

The osmotic-controlled release oral delivery system (OROS) is an advanced controlled release oral drug delivery system in the form of a rigid tablet with a semi-permeable outer membrane and one or more small laser drilled holes in it. As the tablet passes through the body, water is absorbed through the semi permeable membrane via osmosis, and the resulting osmotic pressure is used to push the active drug through the laser drilled opening(s) in the tablet and into the gastrointestinal tract. OROS is a trademarked name owned by ALZA Corporation, which pioneered the use of osmotic pumps for oral drug delivery.

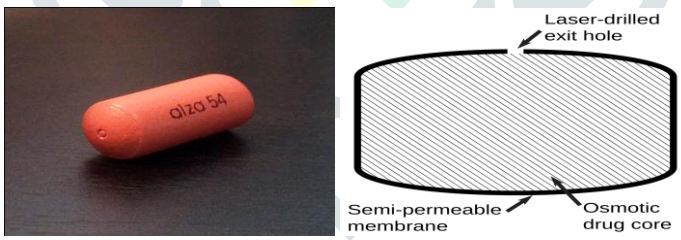


Figure - Elementary osmatic pump

A 54mg tablet of Concerta, which uses OROS technology. 22% of the drug is contained in the red overcoat, while the remaining 78% is split between two drug layers of differing concentration. The tablet uses an additional push layer that expands as water enters the tablet via the osmotic membrane. The drug is expelled via the laser-drilled hole visible on the left side of the tablet. Some example of OROS Medication is Acutrim (phenylpropanolamine) , Adalat OROS (nifedipine) , Alpress LP (prazosin) Cardura XL (doxazosin) , Concerta (methylphenidate) , Covera HS (verapamil) , Ditropan XL/Lyrinel XL (oxybutynin) , Dynacirc CR (isradipine) , Efidac 24 (pseudoephedrine/brompheniramine, pseudoephedrine/chlorpheniramine, pseudoephedrine).

'TIME CLOCK' PHENOMENA –

The time clock phenomenon is a delivery device stranded on solid type dosage form that is covered by an aqueous scattering. The core stuff is coated at elevated temperature with aqueous dispersion of a hydrophobic

category surfactant layer (Beeswax,Carnubawax). A water soluble group coated is applied to improve adhesion to the core coat. Once in contact with the simulated dissolvation fluid,the dispersion media is rehydrated and redisperse. The lag time could be assured by changing the thickness of the applied film. After the lag time mean the time required for rehydration, the core instantly release the loaded API.

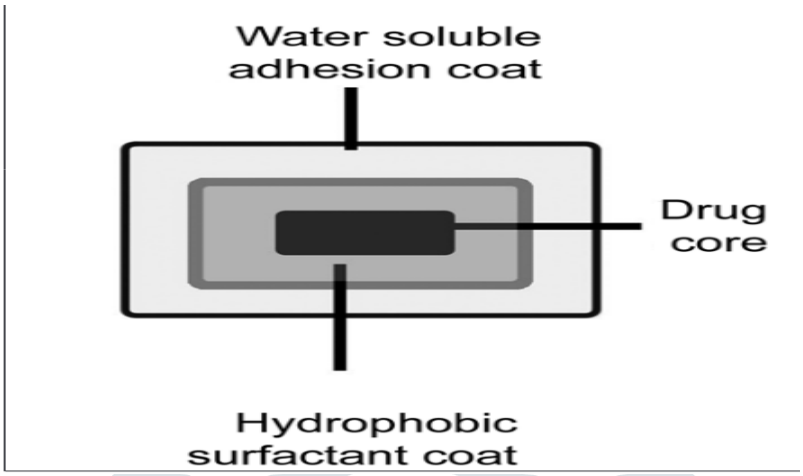


Figure- TIME CLOCK ® PHENOMENA

Conclusion and future aspect :

Oral drug delivery is the largest, oldest and most prime route of administration. It can be accomplished that pulsatile drug delivery system provides a key to the delivery of drug that exhibit chronopharmacological behavior and night time dosing requirement. Ideal PDDS should be self regulating, when taken any time of the day and should take environment factor in account (awake sleep ,light dark, activity rest). Eg the human body is comprises of molecule hence the availability of the molecular nanotechnology that facilitated self regulation of PDDS based on body immune system and disease state will permit dramatic program in human medical service. Circadian disorders such as hypertension, osteoarthritis, asthma etc, which require chronotherapy. PDDS can easily solve this problem as it is modulated according to body's circadian clock giving release of drug after specified lag time. Pulsatile drug delivery systems offer a solution for delivery exhibiting chronopharmacological behaviour, broad first-pass metabolism and night time dose is required. The drug is delivering in the system when its definite concentrate is needed as per chronological need. Technologies or design alone do not make a successful product. Technology needed to be implemented in an appropriate design for a successful product. So PDDS should be promising the future.

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