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REVIEW ARTICLE

PULSATILE DRUG DELIVERY SYSTEM-A TECHNIQUE OF DELIVERING DRUG IN ACCORDANCE WITH BIOLOGICAL CLOCK - A REVIEW

Chiluvuru Vani and K. Srinivas Reddy
Student In Institute Of Pharmaceutical Sciences And Technologies Jntuk Kakinada.

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Abstract

Over last 30 years pulsatile drug delivery system has achieved a lot of importance in drug delivery technology. And the reason why this pulsatile drug delivery is gaining importance is because of its strategy of delivering drug molecule at right place, right time. There are certain diseases which are controlled by biological clock of our body and follow circadian rhythms like congestive heart failure, asthma, rheumatoid arthritis ,osteoarthritis, inflammatory disorders and other hormonal disorders, for this type of diseases conventional solid dosage forms like immediate release tablets or modified dosage forms like sustained, controlled release tablets can't give the required therapeutic response and also for such diseases delivering the drug at right time in right amount is very important. And that task is accomplished by this pulsatile drug delivery system. These pulsatile drug delivery framework is planned by the organic mood i.e., biological rhythms of the body, and medication conveyance is worked with by as per disease cadence. The rule for the utilization of pulsatile drug delivery of the medications is the place where a consistent drug discharge isn't wanted. The principle for the utilization of pulsatile release of the medications is the place where a steady drug discharge isn't wanted, yet drug release must be planned in such a way that, quick medication discharge is accomplished after the lag time. Current review examined the clarifications for improvement of pulsatile drug delivery framework in accordane with body circadian rhythm, kinds of the illness during which pulsatile discharge is required, order, assessments, benefits, impediments.

Introduction:-

Circadian rhythms are 24-hour cycle based changes which occur physically, mentally and behaviourally. These circadian rhythms are the normal process that occur in relation to the light and dark affects, which is seen in most of the living beings which includes animals, plants, and microbes.[1] And the study of biological rhythms and their mechanism is known as chronobiology. These are three types of mechanical rhythms in our body[30]·Ultradian rhythm – these rhythms generally lasts for shorter period[30]·Infradian rhythm – these rhythms generally have a frequency range greater than a day and last until a week.[30]

Corresponding Author:- Chiluvuru Vani
Address:- Student In Institute Of Pharmaceutical Sciences And Technologies Jntuk Kakinada.

The term circadian rhythm is coined by Franz harberg[29] and was first depicted by Halberg and Stephens in 1959. Our body prepare and hold on to its own circadian rhythm. And those are the natural factors which produce these circadian rhythm.

The important genes that facilitate this process of circadian rhythm are "cytochrome genes", these genes code for proteins that develop in the nucleus of the cell with respect to day and night i.e., the build up of protein within the cell's nucleus increases within night and decreases during the day.A study regarding this was studied on fruit-flies suggested that these proteins support in activation of feelings like wakefulness, alertness, sleepiness.

And most importantly along with these proteins exposure to light at a different time of day also affects this phenomenon of circadian rhythm.[1]An important mechanism of body which regulates the circadian rhythm is "Biological clock". This biological clock can be defined as organism's natural timing devices see figure 1.

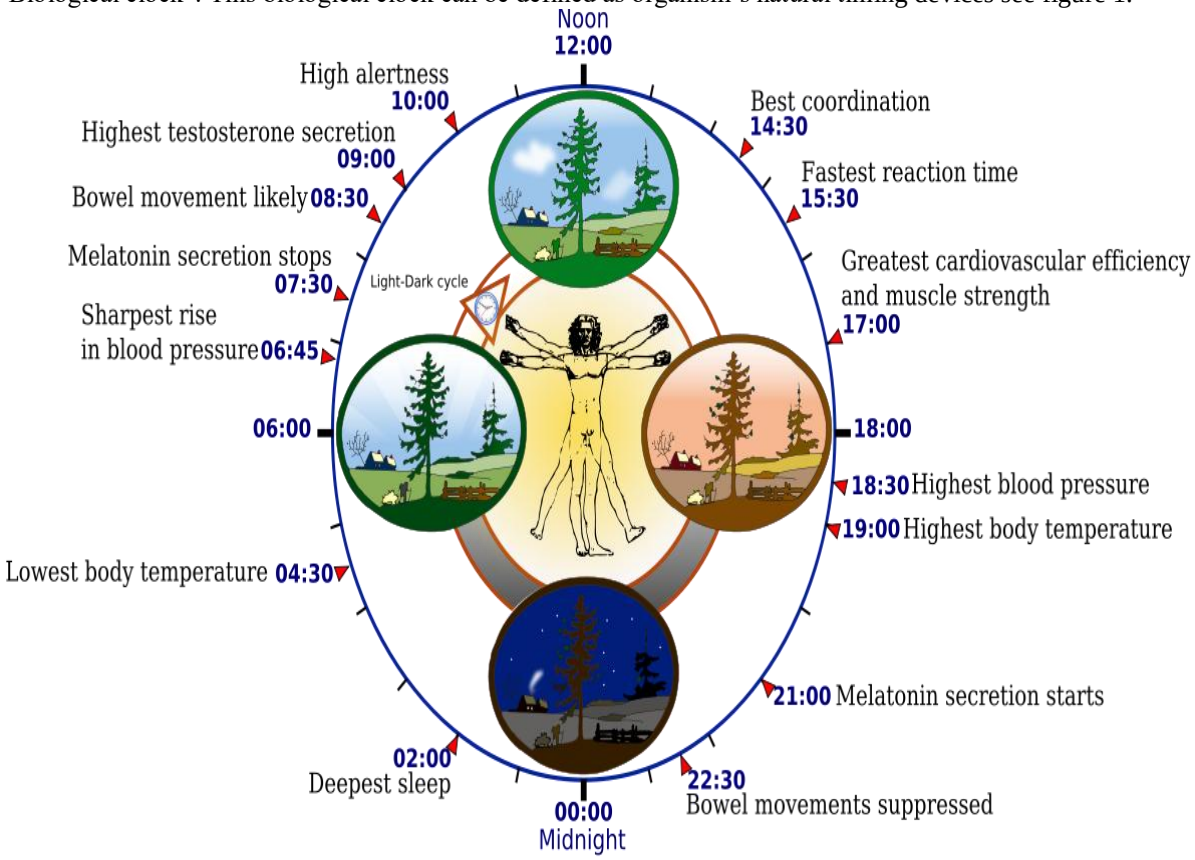


Figure 1:- Circadian Rhythms - internal body clock.

This biological clock is made out of explicit atoms i.e., (proteins) that communicate with cells that are present throughout the body. In human body practically every tissue and organ contains biological clock and through this presence circadian rhythm is regulated by biological clock. Scientists recognised comparative genes in people, fruit-flies, mice, plants, fungi, and several other organisms.[1]

And also there is another clock called "master clock" in brain that organises all the biological clocks and also keeps the biological clock and body in sync.[1]

This master clock in vertebrate animals including humans is a group of 20,000 nerve cells i.e., (neuron) that leads to construction of structure called suprachiasmatic nucleus or (SCN). This SCN is a part of brain called the hypothalamus and gets immediate response as input from eyes.[1]

Circadian rhythm in human body influences so many important functions like see figure 2.

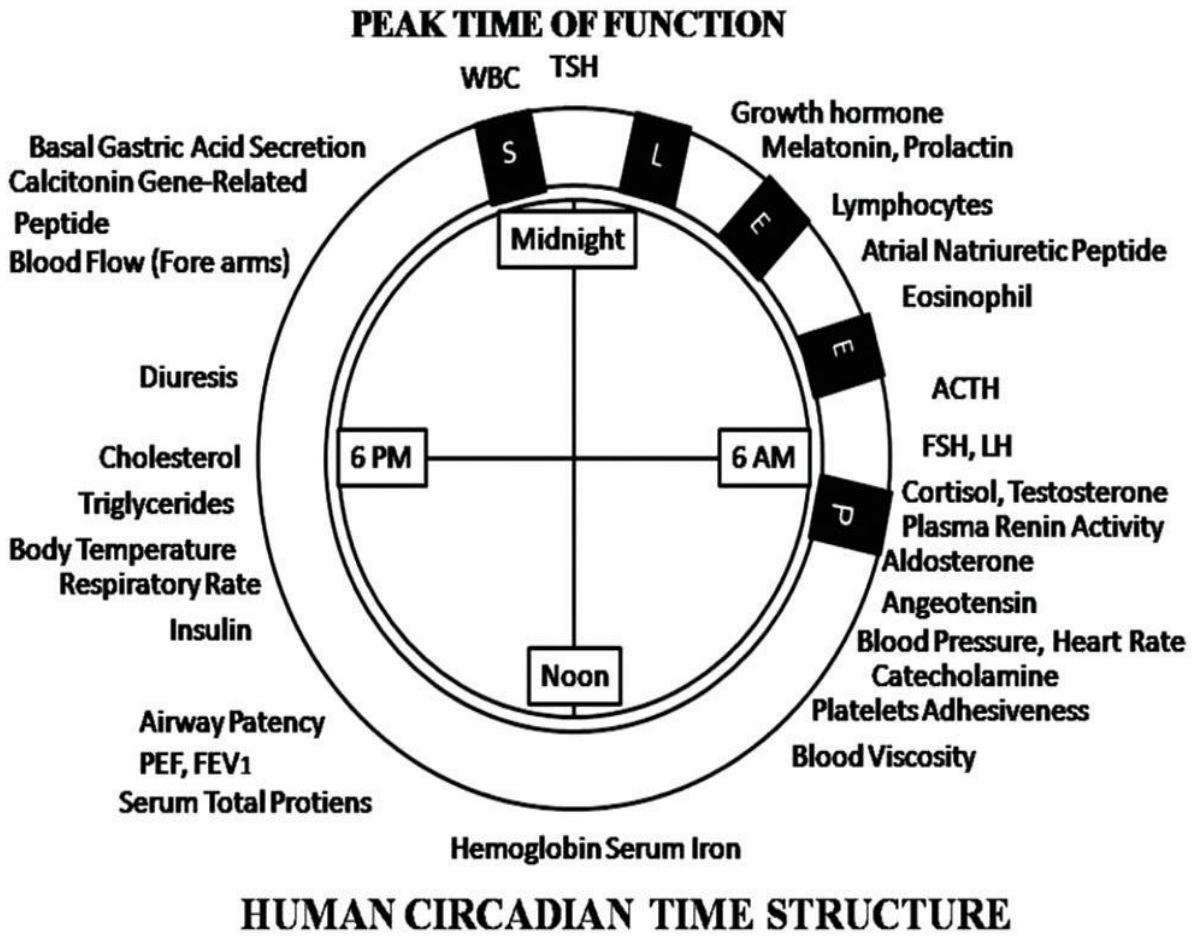


Figure 2:- Human Circadian Time Clock.

1. Hormones
2. Dietary pattern and assimilation.
3. Body temperature

Even then most of the people themselves observe the effect of circadian rhythm on their sleep pattern.
That is suprachiasmatic nucleus control the assembly of melatonin which is a biological chemical substance that makes the person sleepy.This melatonin production is mediated by the SCN which is mediated by approaching light from the optic nerves i.e., when there is low light at night the SCN tells the brain to make more melatonin so person gets drowsy see figure3.

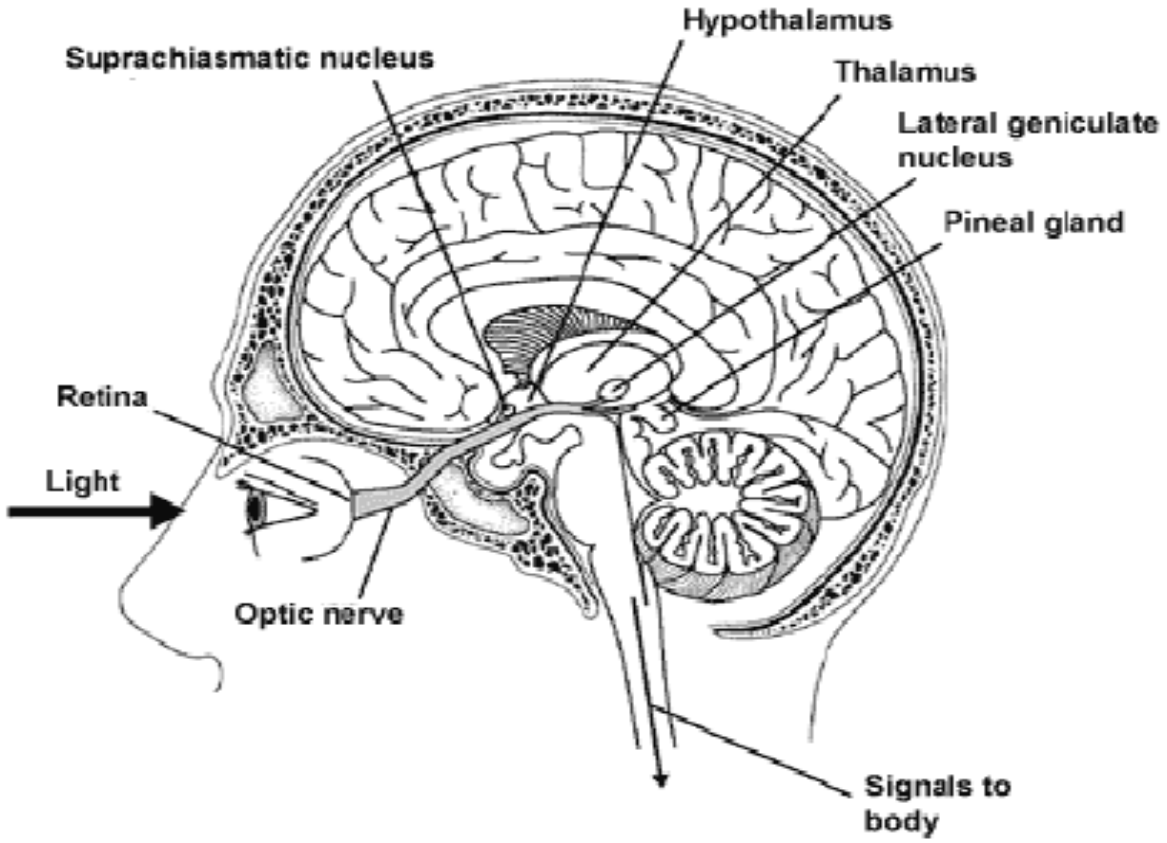


Figure 3:- Indicating biological located in suprachiasmatic nucleus.

Certain progressions may occur in our body circadian rhythms due to variations in our body and environment factors there by these changes in circadian rhythms produce changes that results in sleep disorders and even lead to several chronic health conditions, such as obesity, diabetes, depression, bipolar disorder and seasonal affective disorder.

Every one of these impacts and wonder of circadian rhythms is concentrated by researchers by considering people and by utilizing organic entities with comparative natural clock qualities, like foods grown from the ground. Indeed, even now research is going on by the researchers doing the examinations with controlling the subject's climate by modifying light and dull periods. There by researchers search for changes in qualities movement and other atomic signs. At last the comprehension of this natural check help in creating treatment for jetlag, rest issues,emotional well-being messes and other medical issues.

And also learning more about this biological clock, circadian rhythm helps in more understanding about human body.

Role of Circadian rhythm in phenomenon and severity of diseases:

Most of the medical conditions that occur in our body even the symptoms of those life intimidating medical emergency exhibit a precise timings like,

1. Gout, gallbladder a peptic ulcer attacks occur most frequently in night.
2. Acute pulmonary edema, congestive coronary failure and asthma worsen nocturnally.
3. Sudden infant death syndrome, symptoms of rhinitis and atrophic arthritis are more intense either overnight or within the morning upon wakeing up.
4. Migraine headache is usually triggered during dark sleep or with in early morning times after wakeing up due to rapid eyeball movement (REM).
5. Angina pectoris, ventricular arrhythmia, acute myocardial infract sudden cardiac death stroke, fatal pulmonary embolism and hypertensive crises are most persistent in morning time.

6. Cardiovascular conditions, depression is most grievous in the mornings.
7. Symptom of osteoarthritisdeteriorate during the daily activity, typically intense in the late afternoon and evening.
8. Puncture and draining ulcer is seen to be common during afternoon times.
9. Some type of seizures are triggered during certain sleep stages (or) by transitions between sleep and wakefulness.

Several studies and their reports regarding circadian rhythms state that biological processes are not constant but changes/varies as per time.[12]

Biological rhythms produced by the biological clock are heavily influenced by clock genes like PER1, PER2, PER3, CLOCK, BMAL1, TIM, CRY, CRY2, and TAU.

Through these genes biological clock facilitates fringe oscillators for function like cell proliferation and cellular metabolism.

Among all the genes mentioned above, are divided in to two complexes on functional basis like 1. CLOCK/BMAL1 complex

PER1/PER2/PER3/CRY1/CRY2/TIM complex.
In these two complexes, first complex i.e., is CLOCK/BMAL1 complex promote the transcription of PER.And the activation of PER transcription by CLOCK/BMAL1 complex is inactivated by complex no-2 i.e.,. PER1/PER2/PER3/CRY1/CRY2/TIM. PER is a "pineal body period genes" which is essential for "melatonin secretion". The above mentioned complexes act by "negative auto-feedback system, it is clear that these complexes plays an essential role in generation of circadian oscillation. Through these genes biological clock create signals of circadian rhythm; these signals are directed to the "supracervical sympathetic nucleus and pineal body". These generates signals by biological clock nothing but biological rhythm deal with the control of biological rhythm deal with the control of biological functions like " autonomic nerve frame work, endocrine system and immune system.

All of these systems are fundamental in maintenanceof homeostasis and in providing security against various diseases and administration of medicine may also affect the person against various diseases as per the logical of peak timings of several diseases as mentioned above.

There are cases where certain diseases alter the biological rhythm structure of physical body, which results in prominent changes in response to therapy. Even invention of sustained and constant release systems strategies are not seemed to be applicable in certain cases like the time customised regimeof hormones and many Drugs. There comes the "pulsatile drug delivery system" which can satisfies the requirement.

Pulsatile drug delivery system can be defined as a system where the "drug release after a lag time is consistent with biological time of diseases" See figure 4.

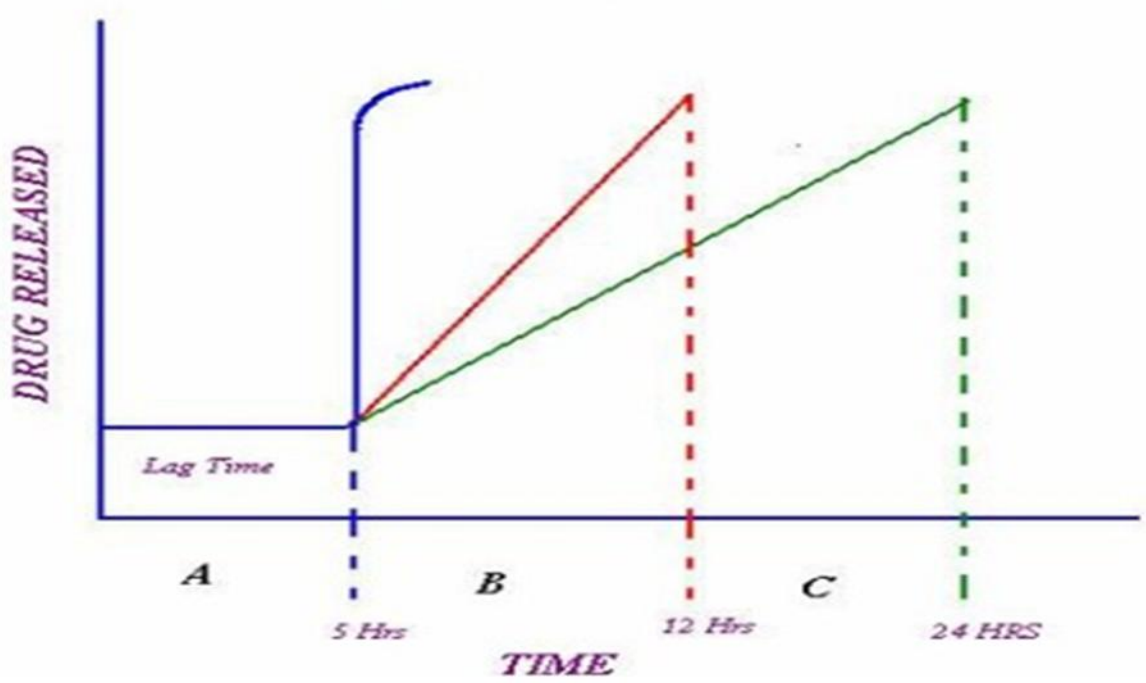


Figure 4:- plot indicating the drug release pattern in pulsatile drug delivery system.

This type of drug delivery frame work is reasonable in conditions of administering "proteins and peptides" which undergo metabolic degradation and in cases of chronic treatment. This method of drug delivery is also suitable for drugs which undergo extensive first-pass metabolism and for drugs which need to be targeted to specific sites in any parts of body.

Eg: intestinal tract- [Development of pulsatile device for specific colonic delivery] this resulted in plasma peak achievement at optimal time, and decrease in number of doses perday and it is saturable with first pass metabolism. And drug tolerance can also be avoided.[12]

Every dosage form is designed to achieve certain targets and by eliminating drawbacks of existing drug delivering systems. Simultaneously for applying any strategy of drug delivering to any drug that drug (or) active pharmaceutical ingredient need to meet certain criteria's as per that drug delivering system. Similarly drugs being selected for pulsatile drug delivery system need to meet certain criteria's. They are like,

1. Drugs that are not reasonable for constant release are suitable for pulsatile drug delivery.
2. Drugs with more toxic effects.
3. Drugs which are tend to exhibit tolerance.

Drugs which are not reasonable for constant release may exhibit rhythmic variation within a circadian cycle and as the basic principle of pulsatile drug release is this, such drugs even add extra benefit i.e., which superficially does not need any modifications. And if drug possess more toxic effects, and if it is taken for steady medication discharge pattern it even more increase the exposure of body tissues towards this drug thereby exhibiting toxic effects at greater extent.

If Drugs exhibiting tolerance upon constant drug exposure in such cases constant drug release systems has more tendency to gain tolerance within short span. So taking such drugs as pulsatile drug delivery frame work helps in overcoming the natural drawbacks of drug.[5]

Influence of circadian rhythms on pharmacodynamics and pharmacokinetics

Chronopharmacodynamics:

In body biological rhythms at the cellular and subcellular levels produce a significant dosing time variations in the pharmacodynamics of therapeutic regimen which are actually unrelated to the pharmacokinetics, and this phenomenon is called "chronoesthesy".

Drug absorption

Circadian commute in drug assimilation are dependent on Gastric acid secretion and pH, motility, gastric emptying time, and gastrointestinal blood flow. These factors vary with time in a day. And that leads to changes in dosing time-dependent difference of drug absorption.

Eg: If circadian changes occur with respect to p^H it results in circadian changes of drug ionization depending on its physicochemical properties. Circadian changes with regards to drug absorption is mainly dependent on physicochemical properties of drug mostly lipophilicity and hydrophilicity. Lipophilic drugs are more susceptible to circadian commutes and even route of administration also brings circadian changes in drug absorption.

Drug distribution

Circadian changes with regards to drug distribution are due to circadian changes in biological fluid and tissues which vary with time in a day. Usually sympathetic and parasympathetic responses affect the blood flow with in the body and this responses are controlled by circadian changes like sympathetic activity is more diurnally and less nocturnally. So therefore blood flow increases diurnally and decreases nocturnally which affect the drug distribution.

Drug metabolism

As we all know metabolism is the activity performed by liver in our body. Which is called hepatic metabolism and the metabolism by liver is dependent on hepatic blood flow and enzyme activity. These both hepatic blood flow and enzyme activity are circadian time-dependent. Several chronopharmacological studies shown temporal changes in hepatic drug metabolism, which is observed in conjugation, hydrolysis, and oxidation.

Eg: circadian variations within the urinary 6β-hydro cortisol to cortisol ratio in man show these in the cytochrome CYP3A activity.

Drug elimination[5, 12]

Like in every organ functions kidney functions like glomerular filtration, renal blood flow, urinary pH, and tubular resorption also exhibit circadian time-dependent changes. If we consider circadian rhythmicity on p^H shows ionization modifications of drugs. This results in elimination of acidic drugs after evening administration.
Eg: sodium salicylate and sulfasylazine.

Necessities of pulsatile drug delivery system:

1. For treating diseases whose "pathophysiology" is mediated (or) controlled arrest treatment during sleep.
   Eg: cardiac arrest treatment during sleep.
   Asthma and joint stiffness in early mornings.
2. Drugs which possess extensive first pass metabolism.
   Eg: proteins and peptides
3. Drugs which exhibit high level of tolerance can be given as pulsatile drug delivery system which facilitates in reducing the exposure of drug in the body.
4. Drugs which are needed to be targeted at descending part of gastro intestinal tract. Like colon.
5. Drugs which possess less t½.
   Eg: βblockers
6. For treating diseases which require exact amount of therapeutic dose for magnifying therapeutic benefits and minimizing adverse reactions.
   Eg: inflammatory bowel disease.
7. To protect mucus layer of stomach from specific drugs
   Eg: peptide drugs;
8. Simultaneously protection of drugs from gastric environment of stomach that is acidic P^H.[10]

Ideal requirments of pulsatile drug delivery system:

1. Pulsatile drug delivery system should equate with real time and distinct triggering biomarkers for a given disease.
2. Should be biocompatible and biodegradable.
3. Should be nontoxic upon usage with delivery system.
4. Should exhibit self regulation and adaptive capability to circadian rhythm.[29]

ADVANTAGES OF PULSATILE DRUG DELIVERY SYSTEM:

1. Pulsatile drug delivery system is anticipatable, reproducible with short gastric residence time.
2. Inert and intra-subject variability is less.
3. Scope for enhancement of bioavailability.
4. Minimizes the adverse reactions and drug magnanimity.
5. Risk of local irritation can be minimized.
6. There is no issue of dose dumping.
7. Shows pliability in design of dosage form.
8. Stability can be ameliorated.
9. Patient compliance and patient comfort is enhanced.
10. Shows drug release pattern.
11. Also helps in NDA filing by patent extension thereby overcoming the contention.

DISADVANTAGES:

1. Drug loading is less.
2. Need of excipient is high when compared to other dosage forms.
3. Manufacturing reproducibility and effectiveness is less.
4. Process variables are high.
5. Cost of production is on high.
6. Advanced technology is needed.
7. For manufacturing this type of dosage forms personnel should be trained and competent.

Classification Of Pulsatile Drug Delivery System:
see figure 5[11]

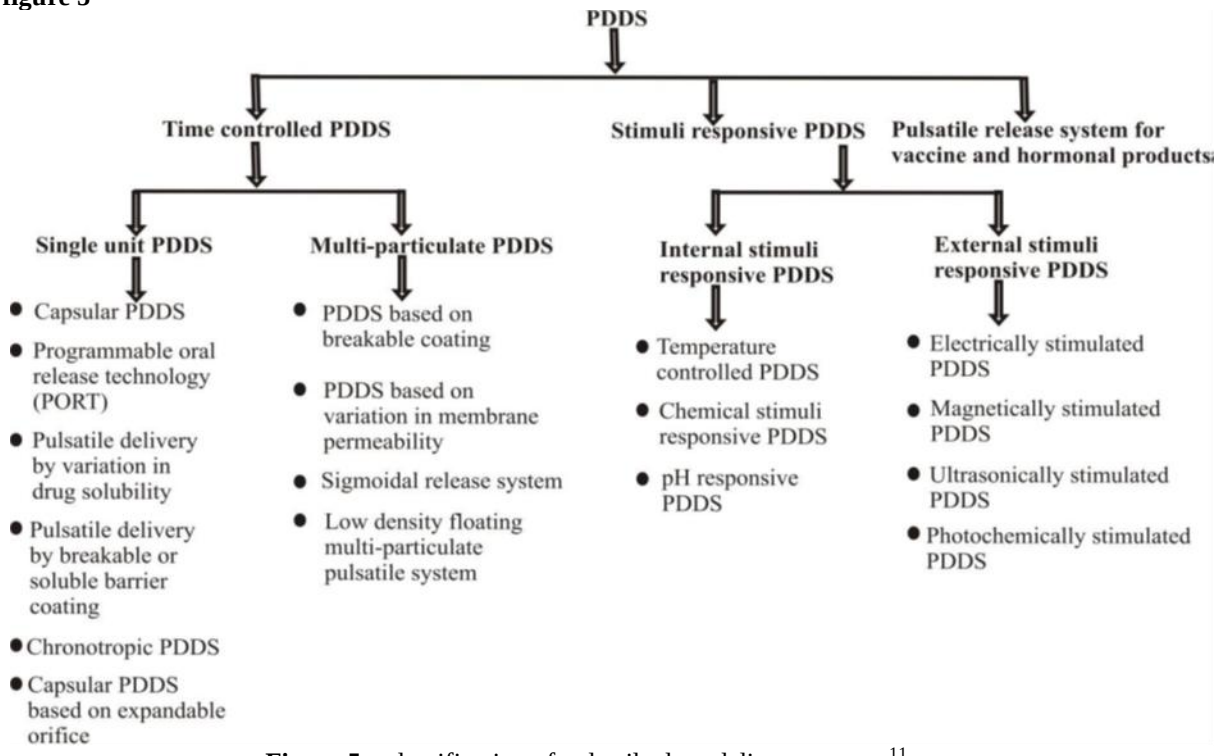


Figure 5:- classification of pulsatile drug delivery system.[11]

I. Time controlled pulsatile drug delivery: (A) Single unit pulsatile systems:
(1) Capsule based systems:Pulisincap system or Single-unit systems are mostly developed in capsule form. The basic principle involved in this type of pulsatile drug delivery system is controlling of lag time of plug present in single unit pulsatile system. There by after a specified lag time by the formulator the plug with in the system gets pushed away by the swelling or erosion mechanism which is mediated by dissolution fluid there after releasing of drug occurs see figure 6.

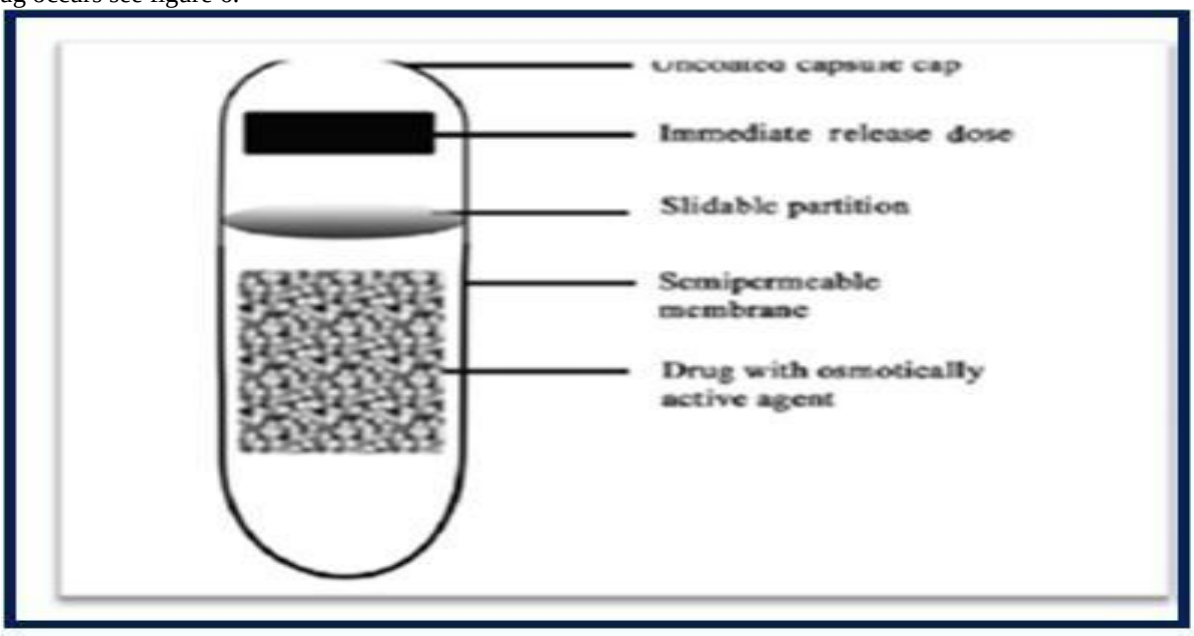


Figure 6:- unit pulsatile system.

This single unit pulsatile system was developed by R. P. Scherer International Corporation, Michigan, US, . This system is designed in such a way that it possess a water-insoluble capsule encasing the drug reservoir. And this water-insoluble capsule which is possessing plug inside upon coming in contact with dissolution fluid the capsule swells by interacting with dissolution fluid and maintains as such till the completion of lag time and there after plug gets pushed out of capsule and making the drug to release from drug reservoir.

The lag time in this system is often controlled by altering the dimension and there by the position of the plug.
Polymers used for designing of the hydrogel plug are as follows.
1. Insoluble but permeable and swellable polymers (e.g., polymethacrylates)
2. Erodible compressed polymers (e.g., hydroxypropylmethyl cellulose, polyvinyl alcohol, Polyethylene oxide)
3. Congealed melted polymers (e.g., saturated polyglycolated glycerides, glycerylmonooleate)
4. Enzymatically controlled erodible polymer (e.g., pectin).
5. The Pulsincap™ device consists of impermeable capsule body containing drug fixed in the capsule with a plug made of hydrogel. This plug swells in GI liquid and exits away delivering drug after an laid out lag time that's constrained by thickness of hydrogel plug.
6. substitute to Pulsincap plug is erodible.[5]

(2) Capsular system based on Osmosis:
(a) 'PORT' System:
The port frame work is planned in such a way that it contains a capsule coated with a semi permeable membrane. Inside this capsule there will be an insoluble plug which contains of osmotically active agent and therefore the drug formulation. And the mechanism involved in this is upon the contact of capsule with dissolution fluid the membrane allow the ingress of water or dissolution fluid and there by development of pressure (osmotic pressure) within the capsule which results in expelling of insoluble plug after a lag time. This port system was progressed by Therapeutic system lab Ann Arbor , Michigan, USA. This type of pulsatile drug delivery system is useful in delivering methylphenidate used in the ministrations of attention deficit hyperactivity disorder as the pulsatile port system see figure 7.

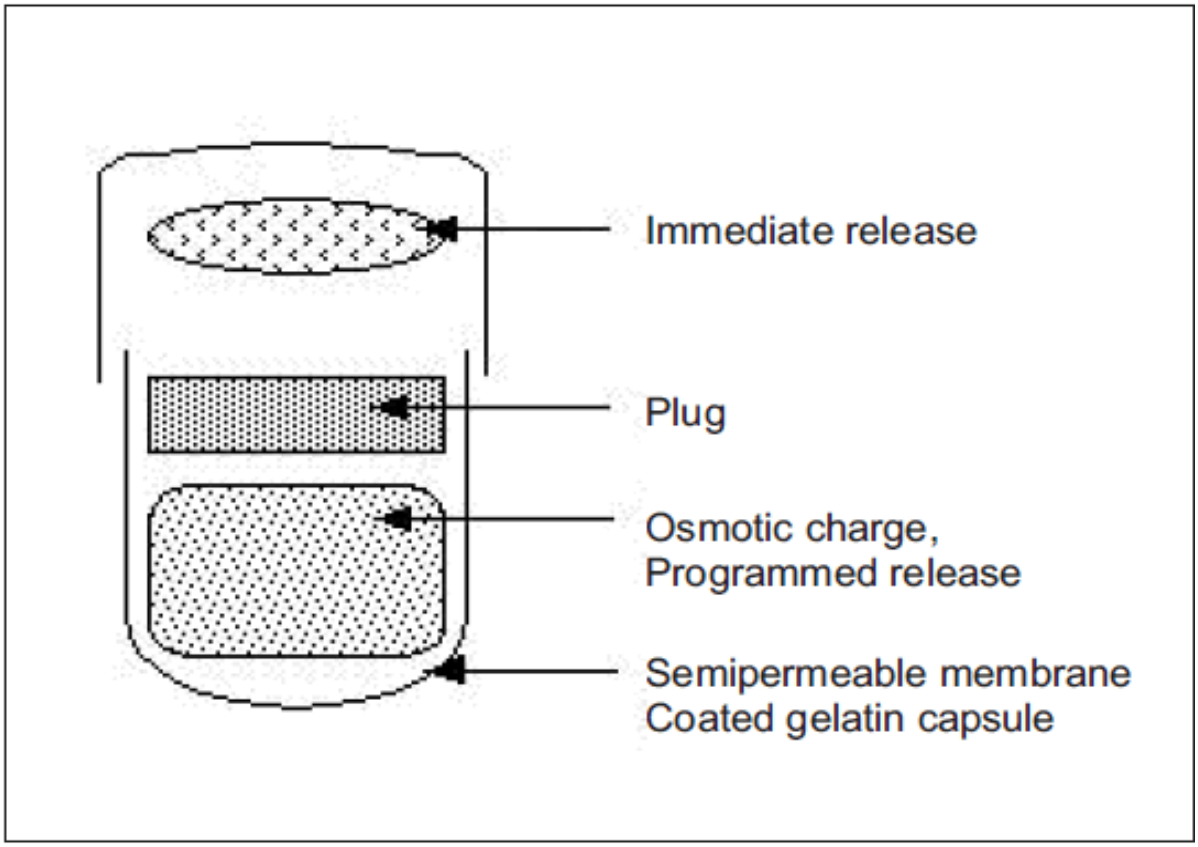


Fig. 3: Plan of Port® system.

Figure 7:- port system.

At the same time this type of system specially in case of delivering methylphenidate helps in reducing the dosing frequency which is major advantage in treating school children during day time.[5]

(b) System based on expandable orifice:

This type of system under pulsatile drug delivery system is invented to deliver drug in liquid form. The liquid drug is formulated in to this by making that liquid drug absorbed in to highly porous particles, these particle liberate the drug through the semipermeable capsule orifice which is supported by an osmotic layer which present next to the barrier layer in dissolved. Delivering the drug in liquid form is the suitable form of drug delivery for insoluble drugs like polypeptides and polysaccharides. This sought of system which is capsular delivers the drug by osmotic infusion of body moisture by capsule, to perform this capsule wall is made up of an elastic material which possess an orifice. The osmosis proceeds to develop the pressure with in the capsule system which make the capsular wall to expand which results in release of drug through the orifice. Upon relaxation of capsule wall the orifice stops the flow of drug. In this system the drug release is attained after lag time of 1 to 10hrs depending on the thickness of the barrier layer. The major advantage with this system is achieving of extended release in addition with high bioavailabilitysee figure 8.

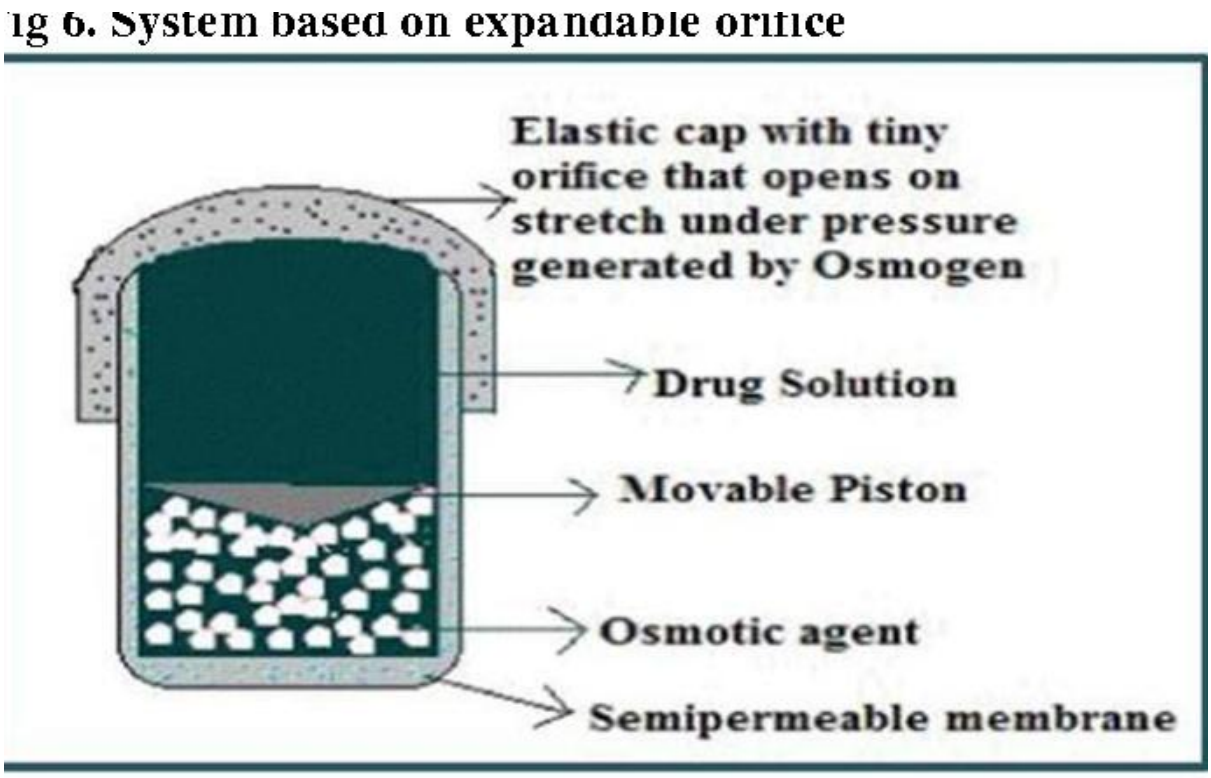


Figure 8:- expandable orifice.

This system can also be used for delivering of drug intermittently at intervals of 6 hours for two days.

(c) Delivery by series of stops:

The main objective of this type of system is for implantable capsules. This system contain two systems which contain drug and water-absorptive osmotic engine respectively. And these compartments are separated by movable slider and that gives pulsatile drug delivery. In this way there will be a series of stops which will barricade the drug release there by providing the lag time which is basic essential for this type of drug delivery. Therefore the amount and frequency with which drug gets released depends on number of stops which were placed longitudinally across the capsule. This type of system is used to deliver porcine somatotropin.

(d) Pulsatile delivery by solubility modulation:

The name itself is self -explanatory that in this system pulsatile drug delivery is attained by solubility modulators.
Eg: salbutamol sulphate which contain NaCl as solubility modulator.
Here in this system the amount of solubility modulator to be taken depend on the saturation to be attained during the entry of fluid in to the osmotic device, hence it is clear that pulsatile drug delivery is dependent on drug solubility. This can be explained in through the above mentioned example that is salbutamol sulphate. This salbutamol sulphate has solubility of 275mg/ml, and 16mg/ml in saturated solution of NaCl. Similarly this NaCl has solubility of 321mg/ml in water, and its saturation solubility is 320mg/ml. This data shows that concentration of solubility modulator depend on the solubility of drug. So here by it is clear that by altering the drug/modulator ration the drug release pharmacokinetics can be altered to zero-order drug release and there by initiating the pulsatile drug delivery. After the period of zero-order release, the drug is delivered as one large pulse.

(3) Pulsatile system with erodible or soluble barrier coatings:

Pulsatile drug delivery system are mostly reservoir system which are coated with barrier layer, this barrier layer erodes or dissolves after a specified time by the formulator which is called lag time which results in release of drug rapidly from a reservoir core. The desired lag time for a formulation is achieved by the formulator by varying the thickness of coating layer.

(a) The chronotropic system:
The Chronotropic system figure 9.

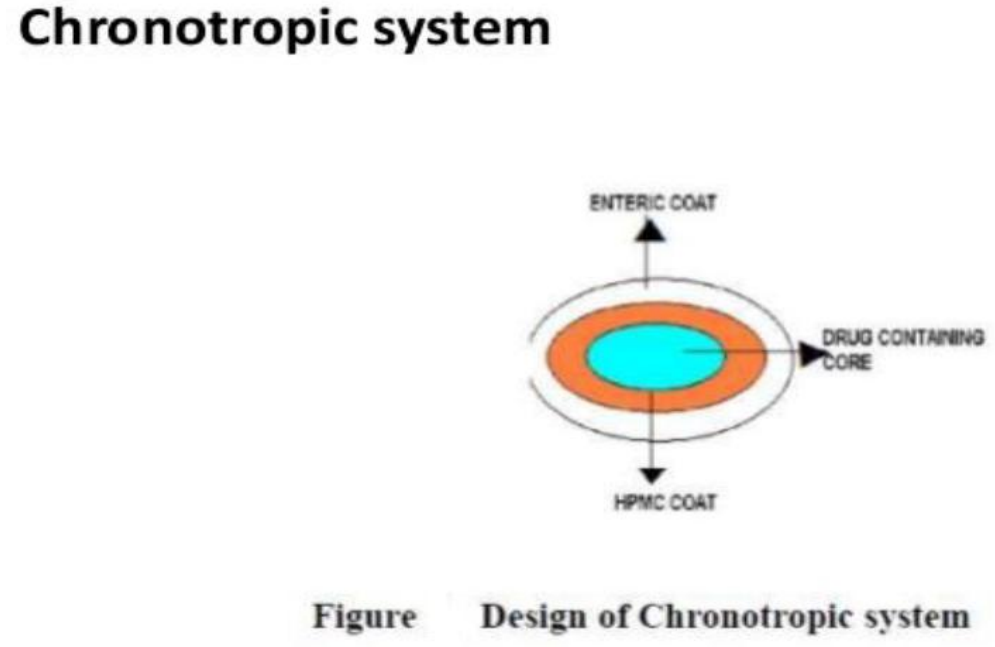


Figure 9:- Chronotropic System.

typically contain drug core coated with hydrophilic swell able HPMC which produces lag period for the formulation.

The main motto of using this different polymers in pulsatile drug delivery is to alter the continuous drug release which is not necessary in treating diseases following circadian rhythm.

Eg: insulin delivery for treatment of diabetes.

In an average human being the production of insulin is generally less, but after intake of meals the insulin production increases. And its natural phenomenon, but in case of diabetic patients the production of insulin is low even after intake of meals. But it is abnormal so in order to treat this insulin is given externally and main intention is to release the right amount of insulin at this specific time. Even in this pulsatile drug delivery system several strategies is used like pumps for pulsatile drug delivery of insulin in case of diabetic patient. But this system throws several problems like serving as pathway for infection because this system require running of tubing across the skin. So another method proposed by Langer and associates exploits the wide tailor ability of biodegradation of the poly (lactic-co-glycolic acid) (PLGA) family of biocompatible polyesters.

In this method by varying the ratios of different copolymers and their relative molecular mass the degradation rate of that material can be varied controllably. And this change in degradation rates of several PLGA copolymers help in bursts release of drug at different times and here they (PLGA copolymers) act as gatekeepers. The drug delivery system in this model is dependent on slow degrading of microchip which is formed from poly (L lactic acid). This microchip is composed of several drug reservoirs and this drug reservoirs are formed by injecting i.e., drug solution microinjected in to an acceptable reservoirs and these reservoirs are sealed with PLGA membranes made of various compositions.

And formulator can form reservoirs of same drug or different drugs. This system exhibits superb high performance along with long time safety and biocompatibility of polymer material. So therefore this system became successful in variety of clinical applications.

The another advanced technique in this model is system which release drug from implant "canin" in response to demand. Further this systems are linked to biosensor devices which makes the drug to liberate in response to physicochemical demand in time.

Eg: If insulin implant is tied to readings from glucose sensor the release of insulin from implant have close control over blood glucose levels in blood thereby reducing the effects of diabetes.

And along with polymeric system delivering drug depending on the "degradation rates" there are polymeric systems whose drug delivery is controlled through externally generated stimuli.

Eg: Thermally responsive polymers using IR using UV.

When compared to polymeric system depending on degradation rates these polymeric systems mediated by external stimuli offer more control and flexibility, but these systems are more difficult and costly affair.[14]
Eg: 1. Formulation and evaluation of chrononmodulated drug delivery of Montelukast sodium.
2. Formulation of floating pulsatile drug delivery system of nifedipine.

Compressed tablets:
In this system of pulsatile drug delivery system, both the drug and coat are compressed other than compressing the core tablet and coating it. In this method the outer layer/outer tablet provides the initial dose of dosage form. And that initial dose is dose given by rapid disintegration and this occurs in gastric region.

The inner core is protected in such way to not to disintegrate in gastric environment but to disintegrate in intestinal environment and this can be achieved by using different cellulose materials. But like any other systems this system posses its own pros and cons like it has an advantage of protecting hygroscopic, light sensitive, acid sensitive drug.
At the same time it has a disadvantage of requiring large amount of coating material and placing the core tablet is difficult.

Multilayer Tablets:
In this system of pulsatile drug delivery system the pulse of two drugs is achieved by compressing two different drugs in two different layers separated by a drug free layer which is made of gellable polymeric barrier layer. And this complete multi-layered tablet is coated on three sides and one side is left uncoated and that is highest layer. This multilayer tablet upon coming in intact with dissolution fluid, the drug gets released rapidly which acts as initial dose.

And second layer which is coated with HPMC layer upon eroding and dissolution in dissolution fluid the drug layer gets exposed to dissolution fluid and drug gets released. And this release or second pulse depending upon rate of gelling (or) dissolution of barrier layer. And for the purpose of barrier layer different polymers are used like hydroxy propyl methyl cellulose, methylcellulose (or) polyvinyl alcohols of different molecular weights.

Advantages over single – unit systems
1. They have little size and there is no danger of dose dumping.
2. There is less inter and intra subject inconsistency in gastro–intestinal transit time.
3. There are less adverse effects and also improved berableness. There is pliability in design and stability also.

Disadvantages
1. Lack of manufacturing reproducibility
2. High production cost
3. Multiple formulation steps
4. Need of advanced technologies.
5. Different types of multi – particulates systems are described below.[19]

Pulsatile system with rupturable coating:
In this system of pulsatile drug delivery the coating layer of core tablet upon rupturing the drug from core is released and this rupturing is the time required is equivalent to lag time. That is period of lag time required can be achieved by varying the different concentrations of polymers.

This rupturing of coating layer can be achieved by different techniques like by incorporation of "effervescent excipients, swelling agents (or) osmotic pressure.

Eg: Let's consider incorporation of effervescent excipient. As we know for effervescence "acid" and "bicarbonate of soda" is required. And this acid and bicarbonate of soda is incorporated during core tablet preparation and coated with ethyl cellulose. And upon intake of this tablet, water enters in to the tablet results in production of co_2 which is end product of reaction of acid and bicarbonate of soda in presence of water. And this production of co_2 from core tablet ruptures coating layer.

And time required for rupturing depend on strength and flexibility of coating layer. If coating layer is of more strength and more thickness and also core tablet of more hardness results in long lag time. In this system the drug release pattern i.e., which is after rupturing of coating layer is similar to immediate release tablets.

Eg: In case of early morning asthma attacks the intake of tablet in that early morning times by the patient is difficult. So if patient take the tablet before bed time the lag time seted by the formulator makes the drug to release to in early morning hours there by preventing the sudden early morning asthma attacks.

Multi particulate/ multi unit system:

1. Pulsatile system with rupturable coating:

The basic mechanism involved in this system is also same as pulsatile system with rupturable coating, but the composition of this varies. That the name itself is self explanatory that it contains multiple units in one system and they are drug coated on no-pariel sugar seeds, Swellable layer, coating layer in ascending order. For swellable system/layer the ingredients used ranges from super- disintegrant like sodium cellulose, sodium starch glycolate, L-Hydroxypropyl cellulose and polymers like PVA.

And the mechanism of drug release is same as discussed in some of above systems like, upon entry of water in to swellablelayer that layer swells and triggers the rupturing of coating layer followed by drug release. This system of drug release is independent of P^H, drug solubility etc.

Lag phase in this system depend on the thickness of coating layer and varying amounts of lipophilic plasticizer with in outermost layer i.e., coating layer see figure 10.

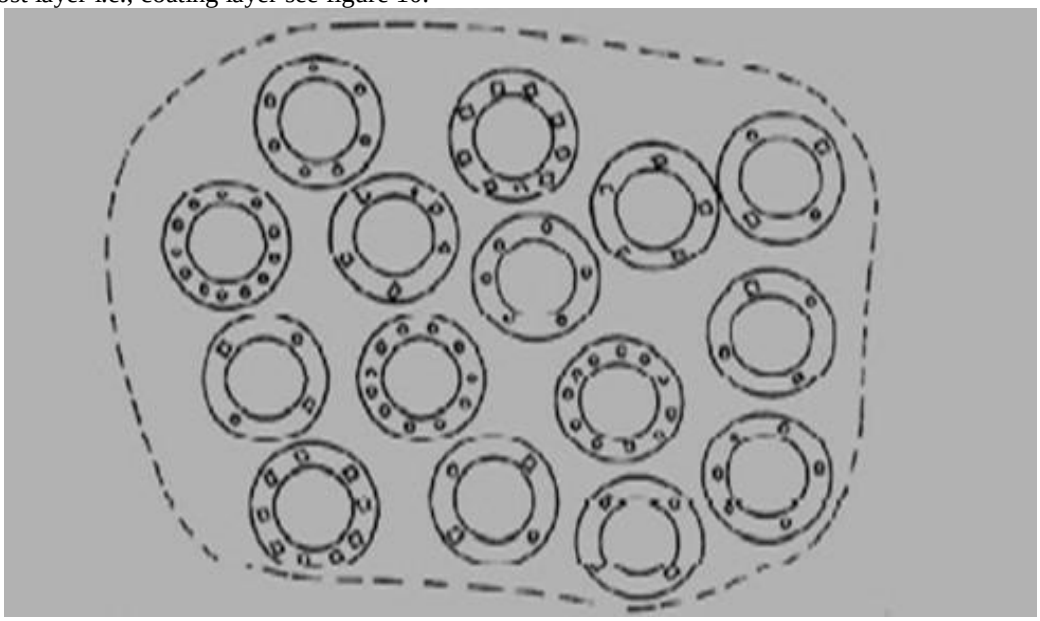


Figure 10:- multiparticulate system.

Eg: 1.Chronomodulaetd drug delivery system of irbesartan for treating hypertension.

2.Chronomodulated drug delivery system of urapidil for the treatment of hypertension by using multiparticulate system.

Osmotic basedrupturable coating system:
Even though the name is osmotic based rupturable coating this system happens to be formulated using two strategies namely osmotic and swellable.

Swelling effect:
The core tablets is formulated in such a way that it contains low bulk density solid (or) liquid which is lipid moiety.
Eg: mineral oil and a disintegrant

And this core tablet is coated with cellulose acetate polymers. Upon intake of this tablet the water enters in to core and displaces the lipid this causes increase internal pressure till a critical stress is reached. This pressure leads to rupturing of coating layer see figure 11.

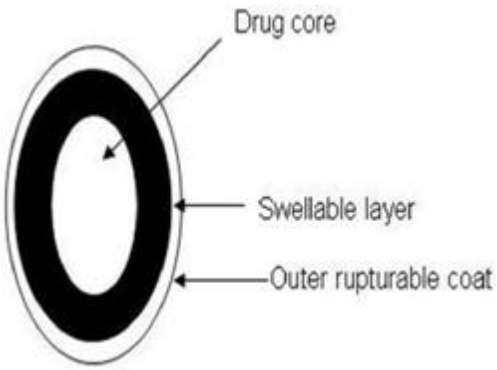


Figure 11:- pulsatile drug delivery based on Rupturable coating.

This is a single unit system, there is another system which contain large number of pellets with different release pattern. In this system each pellet is a single unit and whole tablet/capsule contain several number of such single unit pellets. This core is simultaneously coated with water-permeable, water-insoluble polymer. Each and every pellet differ from each other by the factor called rate of water influx and drug efflux.

The osmotic agent within the pellet dissolves in water leads to the swelling of pellet which results in controlling the speed of drug diffusion. This effect from each and every pellet i.e., drug releasing sequence provides series of pulses of API from same system (or) same dosage form.
Eg: 1.delivering of antihypertensive drug that is diltiazem.
2. Preparation of chronomodulated drug delivery system of captopril.

Pulsatile drug delivery by changes in membrane permeability:
This system is based on changing the membrane permeability usually the membrane permeability of acrylic polymers with quaternary ammonium groups can be influenced by the presence of different counter- ions in the medium which it need to show drug release.

In most of this systems Eudragit is a suitable polymer. This Eudragit contain positively polarized quaternary ammonium group in polymer side chain.

Which is in the middle of negative hydrochloride counter-ions. As the ammonium which is present in the polymer is a water loving group which facilitate the interaction of water with this polymer there by altering the permeability. And this is the property required to achieve lagtime. The lag time is directly proportional to the thickness of coat. At the same time drug release is independent of thickness of coat but results in quantity of salt present in system.

Eg: formulation of pulsatile drug delivery system of metaprolol tartrate using core in cup tablet.
Stimuli induced pulsatile systems:
In this system the release of drug is mediated by stimulation of biological factor like temperature, or any other chemicals stimuli. Depending on these systems are classified in two systems like.
1. Temperature induced stimuli system.

2. Chemical induced stimuli system.

Temperature induced stimuli system:
In this temperature induced stimuli system, thermo responsive hydrogel systems have developed for pulsatile drug release. For this purpose the polymer used undergoes either swelling (or) deswelling in order to produce response to the temperature which brings variance in drug release in swollen state.

Chemical induced stimuli system:
In this system any chemical substance with in the body acts as stimuli. This system is further divided in to different types depending on type of chemical inducing stimuli.

Glucose-responsive insulin release devices:
In diabetes milletus the glucose levels in the body increases rhythmically as a body's natural phenomenon so therefore the injection of insulin should be done at required time by body.

And several systems have developed for this purpose to achieve this target. And one such system among them is the system which possess P^H sensitive hydrogel. This hydrogel is used to place the "glucose oxidase" which is an enzyme through immobilization technique. This system works by "negative feed-back mechanism that is when the glucose concentration within the body increases the enzyme "glucose oxidase" convert the glucose in to gluconic acid. This gluconic acid alters the p^H upon change in p^H the p^H sensitive hydrogel gets swell and results in insulin release.

And that release of insulin reduces the glucose levels in blood there by gluconic acid levels also decrease there by deswelling the hydrogel i.e., it retains to its normal condition.
Eg: For p^H sensitive polymer N,Ndimethylaminoethyl methacrylate, chitosan, polyol etc.,

Inflammation induced pulsatile release device:
When an average human being gets infected with physical (or) chemical stress such as injury, fracture etc, inflammation is produced at that site. During the process of this inflammation "hydroxy radicals" are produced by the "inflammation-responsive cells". And to treat the disease associated with the inflammation (like rheumatoid arthritis, gout etc.) Yui and associates focussed on hydroxy radicals which were produced during inflammation by inflammation responsive cells. And they used "mucopolysaccharide (HA)" and made them to degrade in predetermined manner by "hyaluronidase" or "free radicals". This process of degradation is very low in normal (or) healthy condition.

So they decide to treat this inflammatory response based diseases by incorporating "anti-inflammatory" in HA gels by means of new implantable drug delivery system.

Drugs release from intelligent gels responding to anti-body concentration:
There are various number of bioactive compounds. And in association with this bioactive compounds, novel gels were invented recently which possess the ability to change the concentration of this bioactive compounds there by altering their "swelling and deswelling" mechanisms. This principle is mainly focused to apply in case of "antigen-antibody" complex formation. As the gels which are used in this complex formation in laboratory scale posses specific links for specific antigens, and reversible gel swelling/deswelling the changes in drug permeation are occurred.

P^H sensitive drug delivery system:
This p^H sensitive drug delivery system contain two compartments, one is compartment which shows immediate drug release and the other is compartment which shows pulsatile drug release. As we know a human alimentary canal contain different p^H throughout and to give drug release at specific location in this alimentary canal is difficult but it can be achievable through this p^H sensitive drug delivery system.
Eg: If drug needed to be released in intestine then that formulation need to be released in intestine then that formulation need to be resistant in gastrointestinal p^H and that is done by usage of P^H sensitive polymers. By selecting alkaline sensitive p^H polymer for drug release at intestine then formulation upon entering in to intestine the polymer gets sensitised and release the drug at alkaline p^H.

Examples for p^H sensitive polymers cellulose ester, phthalate, polyacrylates, sodium carboxy methylcellulose etc.

(6) Externally regulated pulsatile drug delivery:

Along with these physical and chemical stimuli, pulsatile drug delivery can also be done using external stimuli like magnetism, ultrasound, electric effect and irradiation.

Eg: magnetically controlled (or) regulated system contain magnetic beads in the implant and upon application of magnetic flux the drug release from implant containing magnetic implant occur.

Need for pulsatile drug delivery system:
All endogenous natural cycles and capacities are customized on schedule during the 24 hour for the lead of explicit exercises at discrete occasions. Various sicknesses show their pathogenomic following an organic cadence.

Asthma:
Circadian changes are found in typical lung work, which drops in the early morning hours. The diminished lung work is more articulated in individuals with asthma. It is generally most noteworthy at 4 pm and least at 4 am. It is the 4 am when asthma is more predominant.
Eg: Formulation of pulsatile drug delivery system of zafrilukast.

Arthritis:
Patients with osteoarthritis will in general have less agony inside the morning and more in obscurity, while those with atrophic joint inflammation, have torment that occasionally tops inside the morning and diminishes for the duration of the day. Proinflammatory cytokines show an exceptional rhythmicity, particularly serum TNF and serum IL-6, and close by other important immunological boundaries show a rise in early morning hours in patients with rheumatoid joint inflammation. Consequently such patients experience joint agony, morning firmness and utilitarian inability in early morning hours. Chronotherapy for a wide range of joint inflammation utilizing NSAIDS ought to be planned to ensure that most noteworthy blood level of medication harmonize with the tallness torment.

Diabetes:
Circadian conduct in glucose and insulin emission in diabetes was uncovered and examined. Expansion in blood glucose level is found after dinner.

Cardiovascular Diseases:
Angina pectoris, ventricular arrhythmia, intense myocardial infarct, unexpected heart demise, stroke, deadly embolism, and hypertensive emergency's all are generally incessant in morning as are other cardiovascular conditions. Cardiovascular occasions in a diurnally dynamic individual accomplishes top in the middle of 6 am to 10 pm see figure 12.

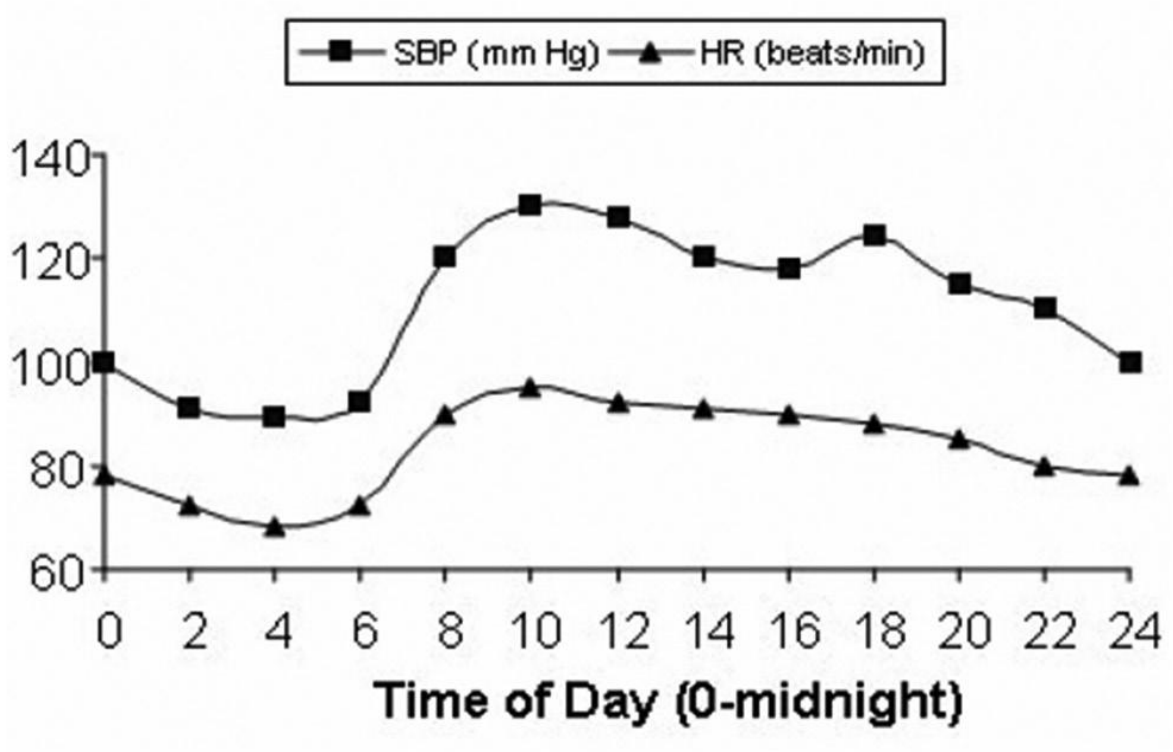


Figure 12:- Indicating Cardiac Events Increases In Early Morning Times In Hypertension Patient.

Recent available different pulsatile drug delivery technologies:

OROS® technology:

Chronset™ is a proprietary formulation for this dosage system. The basic mechanism in this system is osmosis. This system/technology delivers the dose of drug in time and site specific manner. This technology is formulated in such a way that it contain active pharmaceutical ingredient which is surrounded by a laser membrane which is drilled to form orifice. This orifice serves as pathway for release of microspheres containing pharmaceutically active component.

This release of microspheres through orifice is done by a method called "melt-spinning". In this method the complex of "biodegradable polymer" and bioactive agent is subjected to a temperature, mechanical forces and flow rates. This leads to release of microspheres of diameter 150-180µm which are of high drug content. This technology is developed to deliver drugs like "Cardizem RLA", "diltiazem".

CONTINR technology:

This technology contain a matrix which possess uniform porosity (semipermeable matrix). This type of matrix is observed in control release formulation.

This matrix formed by substituting aliphatic group on to the cellulose polymer by solvating polymer with volatile polar solvent followed by reacting that solvated polymer with aliphatic alcohol in melted form. This is the phenomenon (or) process of molecular coordination complexes between cellulose polymer and non-polar solid aliphatic alcohol.

This technology paved a path for development of sustained-release tablets of aminophylline, theophylline, morphine and other drugs.

The control over the amount of drug being released to blood stream is achieved through CONTINR technology. This system helps to improve patient compliance by decreasing dosing frequency.

DIFFUCAPS® technology:
This technology is developed by R.P.scherer international corporation, Michigan, us. And this is an example of multiparticulate technology by reliant pharmaceuticals LLC for chronomodulated drug delivery of two drugs in a single formulation.

This DIFFUCAPS is like a capsule which is administered in to body to deliver two drugs in circadian drug release technology.

This DIFFUCAPS contain particles like (beads, pellets, granules etc) which contain one (or) two pharmaceutically active ingredients. This each pellet releases drug in any form that it provides flexibility of delivering drug in "pre-determined lag time" of three to five hours with pre-designed rapid or sustained release profile through them.

This typical pellet contain acidic (or) alkaline buffer crystal which is inert in nature coated with API in film forming substance. This film should be water-soluble film.

Eg: hydroxy-propyl-methylcellulose, polyvinylpyrrolidine etc. This active core is prepared by granulating/milling/extrusion and spheronizaton of API containing polymer solution.This technology used to formulate drugs like "propranolol" for management of hypertension.

CHRONOTRPIC® technology:
The basic principle of this system is eroding/ solubilising/rupturing of core coated polymer. In this technique, single, multiple solid dosage form like tablet or capsule (or) pellets can be used.

The system contain inner core which contain active pharmaceutical ingredient coated with controlled release layer.

FGALET®technology :
This system contain an impermeable shell which possess two lag plugs. The erosion of this plugs that is time taken for erosion of this plugs is directly proportional to lag time. In between these two plugs there will be a drug. And upon erosion of the plugs the drug in between gets released. Materials used to prepare this shell are slow degrading polymers like "ethyl cellulose" and plasticizer like "cetostearly alcohol". These plugs are made up of pharmaceutical excipients like "polyethylene oxide".

CODAS® technology:
This CODAS is also an example of multiparticulate system. This system contain beads which contain drug. But this are not enteric coated but controlled drug releasing polymer coated with lag time of 5hrs. This controlled drug releasing polymer is combination of both water soluble and water insoluble polymers. In this two polymers water soluble polymer gets dissolved slowly upon getting exposed to gastric fluid. And through this pores the drug diffuses out. And the other polymer that is water insoluble polymer acts as barrier which prevent the bulk diffusion of drug in to gastro intestinal fluid. And this polymer (water insoluble) is responsible for controlled pattern of drug release.

GEOCLOCK® technology:
The geoclock technology has basic idea of applying geo-matrix for achieving pulsatile drug release. And this "geo-matrix" is nothing but a "hydrophilic matrix". This matrix which is a polymer based is coated on either sides (or) both bases of the tablet. This coating on both bases decreases the active surface of core towards the GI fluid there by decreasing/delaying the drug release. And this geo matrix upon exposing to GI fluid it gets swelled and becomes a gel. This gel is not eroded rapidly but erodes slowly which control the process of drug release. This slow erosion time is directly proportional to lag time required. And upon erosion drug layer gets exposed to GI fluid and releasing of drug starts.

PORT ®technology:
PORT can be elaborated as "programmable oral release technologies". The major advantage of this system is that it provides a "multiple programmed release of drug", because of its distinctive coating and encapsulation system. In case of capsule from "active medicament" is combined with osmotic agent and it is kept inside the capsule shell. This capsule shell is closed with "water-insoluble plug". In case of tablet form a polymeric core which is containing API is coated with semipermeable rate controlling polymer.

Three-dimensional printing® (3DP) technology:
Three- dimensional printing technology is an innovative technology. This three dimensional printing technology is used to formulate oral dosage forms which possess more complications in its formulation. This three-dimensional printing technology can be applied to various engineering devices having complicated internal genomics, of different densities, diffusivities and different chemical complexes which are to be delivered orally. And tablets like immediate release, pulse release, break way tablets and dual pulsatory tablets can be formulated using this technology.
Eg: voltaren.

Thus is enteric dual pulsatory tablets. This system is constructed in such a way that voltaren is printed in two separate areas of continuous enteric excipient phase.

And this system showed drug release in two pulses with lag time difference of about 4 hours in in-vitro conditions.

TIMERX®technology:
This system is hydro-gel based system which is a controlled release pattern. This system gives different release kinetics by altering molecular interactions. As this hydro-gel system it contain "xanthum and carob gums" which are mixed with dextrose. In this system drug release is monitored by the rate of water penetration from GI environment in to TIMERX gum matrix; and this expands and convert in to gel and thereby releasing active drug substance.

Physic chemical modification of API:
This is strategy of altering (or) modifying the active pharmaceutical ingredients physicochemical properties like solubility, drug lipophilicity, partition coefficient, crystalline form, membrane permeability, freezing point etc. This modifications can be done by performing (or) utilizing several techniques there by achieving chronopharmaceutical drug delivery.

Controlled- release microchip:
This microchip is made of silicon and it is an alternative to micrometer scale pumps, valves and flow channels, which are associated in delivering single and multiple substances in controlled manner as predetermined in accordance with need of body. The mechanism of drug release of this system is predicted by "electro chemical dissolution" of thin anode membranes which is covering the microreservior of active pharmaceutical ingredient.

Chronomodulating infusion pumps:
Infusion pumps are used for delivering the drug in chronomodulated technology and its application is seen in melodie®, programmable synchromed®, panomat® v5 infusion and the Rhythmic® pumps. And this system is applied in various technologies like pre-programmed systems and systems like enzymatic (or) hydrolytic degradation, $P^{H,}$ magnetic fields, ultrasound, electric fields, temperature, light and mechanical stimulation sensitive. Characteristics of this infusion pumps are "light-weight" (300-500g) for providing precision drug delivery.

Pulsatile drug delivery system containing herbal drugs:
In recent days herbal products are gaining a lot of importance because of effectiveness and less side effects and safety. And because of this several research have been focused to develop chronomodulated technology in herbal drugs.

Eg: 1. Sarfaraz and joshi focused for development of this technology in herbal drugs and developed a chronomodulated solid dosage form i.e., tablet containing "Adhatodavasica" (vasaka powder) for treating and prevention of asthma attacks in early mornings. And this tablets were evaluated and optimised and such formulation is coated with ethyl cellulose as inner layer and Eudragit S 100 as outer enteric coating layer.

Dissolution studies showed 91.46% drug release in p^H 6.8 at the end of 10hours.

2. Li.et formulated and developed a pulsatile tablet with a compound which is official in china called danshen. Danshen is a compound used to treat cardiovascular disorders. And in this formulation three combination of herbal drugs are used like 1. Danshen(root of silvia miltiorhizabge), 2. Sanqi (root of panaxnotoginseng) and 3. Binojpian (dryobalanopa aromatic).

All these drugs are prepared in 3 layer contaning “sodium carboxy methyl starch, microcrystalline cellulose, succinic acid, and lactose” are employed as excipients for this dosage form.

Eudragit RL, HPMC, is a major components of the separation layer. And mixture of ethylcellulose and Eudragit RS and RL are the important and basic components of selling and control release layer. This system showed the lag time with a range of three to eight hours in in-vitro dissolution study.

Disease	**Chronological Behavior**	
Asthma	Bronchial asthma is a state of the lungs which is portrayed by intermittent, reversible choking of the bronchi because of the fixing of encompassing smooth muscle. The lion's share of bronchospastic assaults happen in early morning (2 to 6 am)	Salbutamol Sulphate (Pulsatile Pellets) [49], Theophylline (Pulsatile press-coated tablet) [50]
Peptic ulcer	Peptic ulcer is an unmistakable necrosis in the mucosal covering of the stomach (gastric ulcer) or the first part of the small digestive tract (duodenal ulcer) and an after effect of sharp impacts of acid pepsin in the lumen and amazingly agonizing. Helicobacter pylori are quite possibly the most widely recognized reasons for peptic ulcer. The side effects of crrosive discharge emerge after mid evening (2 to 4 am)	Ranitidine Hydrochloride (Floating pulsatile tablet) [51], Famotidine (Osmotic tablet) [52]
Cardiovascular Disorder	A cardiovascular problem portrays an ill-advised working of the heart or veins. The stream of blood to mind, heart or body can be decreased because of blood clump (apoplexy) and plaque buildup in the dividers of supply routes prompting the solidifying and narrowing of courses. In nocturnal hypertension platelet pleasantness expansions in early morning.	Lisinopril (Osmotic pulsatile tablet) [53], Amlodipine Besylate (Pulsatile tablet) [54], Felodipine (Pulsatile tablet) [55]
Diabetes mellitus	A gathering of metabolic issue in which the individual has high glucose level in the blood can be named as diabetes ellitus. The explanations for the increment glucose level in the blood all things considered as a result of deficient insulin creation or due to the body's cells doesn't react as expected to insulin.	Glibenclamide (Pulsincapmicrosponges) [56], Glipizide (Pulsatile Pellets) [57], Insulin (Pulsatile Liposomal system) [58]
Arthritis	arthritis is a type of joint problem and that includes aggravation in more than one joints. The most normal sort is osteoarthritis and it brings about injury and contamination of the joints. In osteoarthritis ligaments loses its	Aceclofenac (Floating pulsatile microspheres) [59], Celecoxib (Osmotic tablets) [60], Diclofenac (Pulsatile microcapsules) [61]

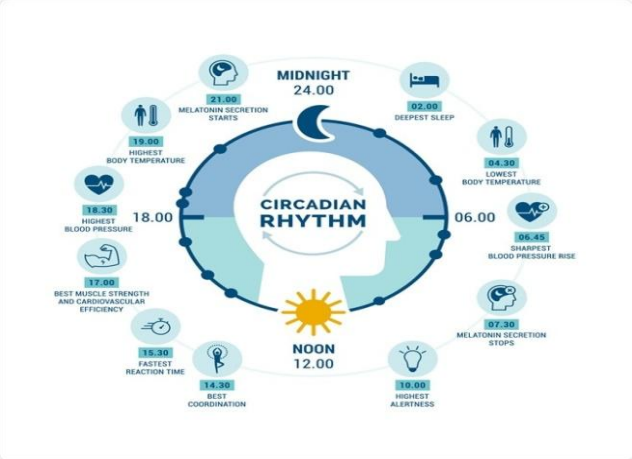
	versatility and get harmed, because of which stringy tissue and tendons become extended and the bones may rub against one another causing serious agony.	
Hypercholesterolemia	Hypercholesterolemia might be named as the increment in the cholesterol level in the blood and the cholesterol union increments during the evening. The cholesterol levels are accounted for to be least at 2 pm to 6 pm and top at 6 am. chronotherapy can be accomplished by timing the prescription as per circadian mood for hypercholesterolemia. The evening dosing of these needs is more compelling than early daytime dosing.	Simvastatin (Pulsatile microspheres) [62]
Cancer	There are many clock genes transcriptional and post transcriptional enactment and restraint of administrative circles that produce circadian rhythms in mammalian cells. The anomaly in the circadian motions emerges in the early morning and to control these motions extraordinary drugs was examined to drag out gastric home opportunity to target stomach disease and increment in drug bioavailability.	5-Fluorouracil (Pulsincap) [64]
Hormone secretion	A hormone is a class of administrative biochemical that created by organs in all multicellular creatures and moved by the circulatory framework to an objective organ to organize its physiology and behavior. Chemicals direct an assortment of physiological and social exercises including assimilation, stress, breath, tissue work, lactation, development and multiplication. The development chemical and melatonin delivered at evening time and testosterone or cortisol in morning hours.	Budesonide (Micro-particles) [65], Fluticasone furoate (Nasal spray) [66]

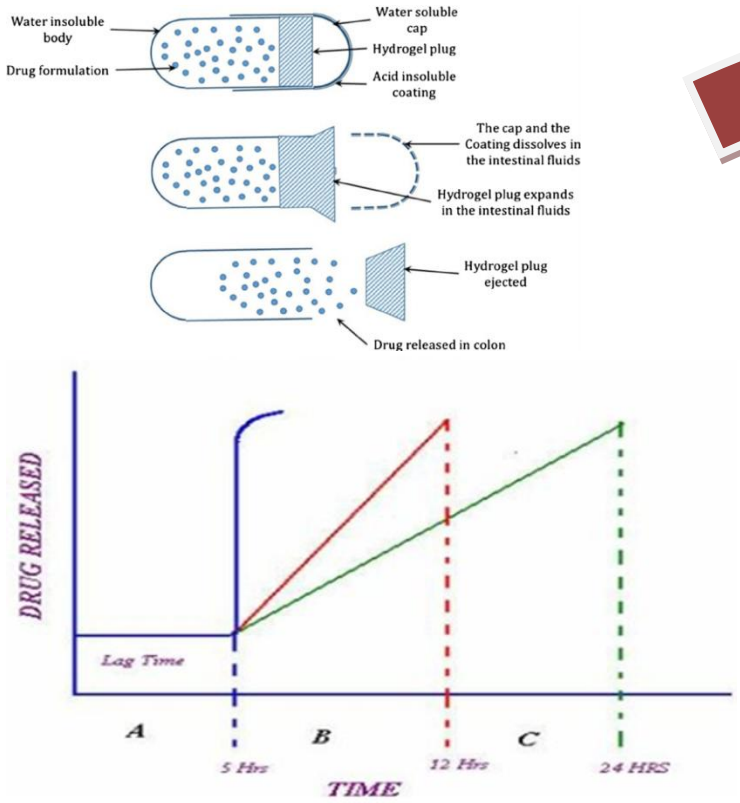
Table 1:- List of diseases and disorder treated according to chronological behaviour by PDDS.

Conclusion:-

Pulsatile drug delivery system main aim is to deliver the right amount of drug, at right time, at right site, in accordance with pulsatile mechanism of disease and body. As we understood that many diseases that attack the humans follow specific pulsatile mechanism. So it is also important and necessary to deliver the drug according to that phenomenon (or) mechanism rather than just delivering generalised immediate (or) controlled release dosage forms. And solution for that is delivering the drug through pulsatile drug delivery system. This pulsatile drug

delivery system gives promising response to so many diseases there by achieving the patient compliance. And also among different types of pulsatile drug delivery system "multiparticulate pulsatile drug delivery system" shows good and better response than "single unit-dosage form". So here by I conclude pulsatiledrug delivery gives promising drug delivery (or) therapeutic efficacy for disease that follow non-constant dosing therapies like diabetes, cancer, asthma etc. Which gives better patient compliance and therapeutic outcome.





Additional file - 1

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