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A REVIEW OF PULSATILE DRUG DELIVERY SYSTEM

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Abstract:

Pulsatile drug delivery systems are gaining importance in the field of pharmaceutical technology as these systems deliver the right dose at specific time at a specific site.the product follow a sigmoidal drug release profile characterized by a time period of no release (lag time) followed by a rapid and complete drug release. diseases where in chronopharmaceutics are promising include asthma,peptic ulcers, cardiovascular diseases, arthritis, neurological disorders and hypercholesterolemia etc. various capsular, osmotic, single and multiple unit systems that are modulated by soluble (or) erodible polymer coatings, rupturable membranes are available in market. These systems are beneficial for diseases showing chronopharmacological behavior where night time dosing is required (or) for the drugs having high first pass effect (or) having site specific absorption in GIT, (or) for drugs with high risk of toxicity (or) tolerance.these systems also improve patient compliance by decreasing dosing frequency.

Keywords: *Chronotherapeutics, Pulsatile Drug Release, Lag Time, Time Controlled Systems.*

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INTRODUCTION:

Now-a-days, the emphasis of pharmaceutical researchers is turned towards the development of more efficacious drug delivery systems with already existing molecule. Modified release dosage forms have a great importance in this regard. Such systems control the release pattern of drug, either with constant or variable rates drug is released with predetermined release rates. However, there are certain conditions for which such a release pattern is not suitable. These conditions demand release of drug after a lag time. This condition can be achieved by pulsatile drug delivery system which is defined as the rapid and transient release of certain amount of molecules within a short time period immediately after a predetermined off- release period i.e. lag time. Time-controlled systems or sigmoidal release systems (Fig 1). A pulse has to be generated in such a way that a complete and rapid drug release is achieved after the lag time so as to match body's circadian rhythms with the release of drugs1.

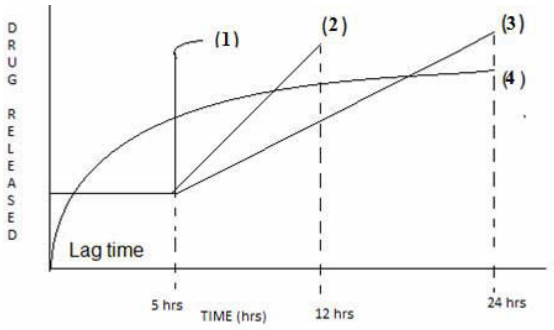

Fig 1: Schematic representation of different drug delivery systems where (1) sigmoidal release after lag time (2) delayed release after lag time (3) sustained release after lag time (4) extended release without lag time.

The "Chronopharmaceutics" consist of two words chronobiology and pharmaceutics. Chronobiology is the study of biological rhythms and their mechanisms.

There are three types of mechanical rhythms in our body. These are:

1.Ultradian Rhythms: Shorter duration oscillations are termed as Ultradian Rhythms (more than one cycle per 24 h). E.g.90 minutes sleep cycle.

2. Infradian Rhythms: Oscillations that are longer than 24 hours are termed as Infradian Rhythms (less than one cycle per 24hours) e.g. Monthly Menstruation**.**

3. Circadian rhythms: Circadian rhythms are self-sustaining, endogenous oscillations that occur with a periodicity of about 24 Hours.

Peak time of various biological processes:

The figure below shows the peak time of biological processes that follow circadian behavior in persons adhered to daily day time routine activity i.e. 6 am to 10 pm. The intensity of symptom of many medical conditions follow in time during 24 hour schedule and severity of diseases exhibit a definite time of occurrence in 24 hour. Peak time of human diseases exhibiting circadian rhythm.

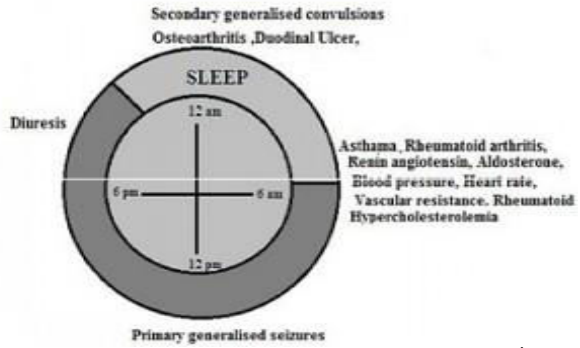

FIG.2 : CYCLE OF CIRCADIAN RHYTHM [4].

Advantage of pulsatile drug delivery system4, 5

1) Due to its ability to release drug in a burst manner, it increases absorption and bioavailability at target site of absorption.
2) Limit risk of mucosal irritation
3) Loss of drug by extensive first pass metabolism is prevented.
4) Chronotherapy, programmed delayed release provides optimal treatment of diseases.
5) No risk of dose dumping.
6) Avoidance of undesirable side effects.
7) Improved patient compliance.

Disadvantage of pulsatile drug delivery system6

1) Low drug loading capacity and incomplete release of drug.
2) Higher cost of production.
3) Large number of process variables.
4) Lack of manufacturing reproducibility and efficacy.

Need of Pulsatile drug delivery8:

a) Body function that follow circadian rhythms.
b) When circadian rhythm is altered by the hormone such as rennin, aldosterone and cortisol etc level in blood.
c) When rhythmic variation seen in acid secretion in stomach, gastric emptying, and gastrointestinal blood transfusion.
d) Disease like bronchial asthma, myocardial infraction, angina pectoris, rheumatic disease, ulcer, and hypertension display time dependence.
e) The lag time is essential for the drugs that undergo degradation in gastric acidic medium.

f) It is possible to deliver the drugs to the distal part of GIT like colon targeting with pulsatile drug delivery.
g) Drugs that undergo extensive first-pass metabolism are administered successfully as pulsatile drug delivery systems.

Classification of Pulsatile Drug Delivery Systems: [1-6]

I. Time controlled pulsatile drug delivery:

(A) Single unit pulsatile systems:

1. Capsule based systems:

Pulisincap system Single-unit systems are mostly developed in capsule form. The lag time is controlled by a plug, which gets pushed away by swelling or erosion, and the drug is released Pulsincap (**Fig. 2**) was developed by R. P. Scherer International Corporation, Michigan, US, and is one such system that comprises of a water-insoluble capsule enclosing the drug reservoir. When this capsule comes in contact with the dissolution fluid, it swells; and after a lag time, the plug pushes itself outside the capsule and the drug is released rapidly. The lag time can be controlled by manipulating the dimension and the position of the plug. Polymers used for designing of the hydrogel plug are as follows.

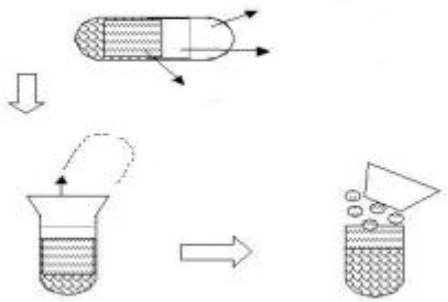

FIG. 3: DESIGN OF PULSINCAP,SYSTEM

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, glyceryl monooleate)
4. Enzymatically controlled erodible polymer (e.g., pectin).
5. The Pulsincap™ device consists of impermeable capsule body containing drug sealed in the capsule with a plug made of hydrogel.This plug swells in GI fluid and exits away releasing drug after a defined lag time that is controlled by thickness of hydrogel plug.
6. Alternative to Pulsincap plug is erodible.

(2) Capsular system based on Osmosis:

(a) 'PORT' System:

The Port system (**Fig.3**) was developed by Therapeutic system research laboratory Ann Arbor, Michigan, USA, and consists of a capsule coated with a semi permeable membrane. Inside the capsule was an insoluble plug consisting of osmotically active agent and the drug Formulation. When this capsule came in contact with the dissolution fluid, the semipermeable membrane allowed the entry of water, which caused the pressure to develop and the insoluble plug expelled after a lag time. Such a system was utilized to deliver methylphenidate used in the treatment of attention deficit hyperactivity disorder as the pulsatile port system. This system avoided second time dosing, which was beneficial for school children during daytime.

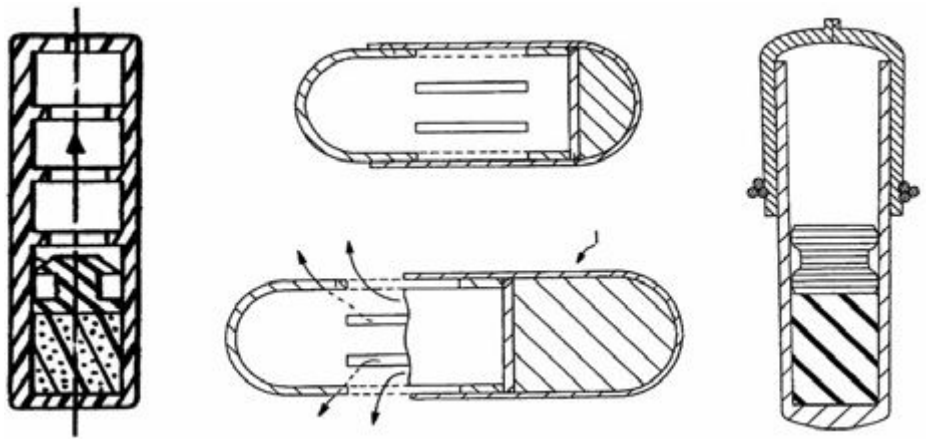

FIG. 4: OSMOTIC PUMPS USED FOR PDDS

(b) System based on expandable orifice:

To deliver the drug in liquid form, an osmotically driven capsular system was developed in which the liquid drug is absorbed into highly porous particles, which release the drug through an orifice of a semi permeable capsule supported by an expanding osmotic layer after the barrier layer is dissolved. This system has combined benefit of extended release with high bioavailability. Delivering drug in liquid form is suitable for insoluble drugs, Polypeptides and Polysaccharides. The capsular system delivers drug by the capsule's osmotic infusion of moisture from the body.The capsule wall is made up of an elastic material and possesses an orifice. As the osmosis proceeds, the pressure within the capsule rises, causing the wall to stretch. The orifice is small enough so that when the elastic wall relaxes, the flow of the drug through the orifice essentially stops, but when the elastic wall is distended beyond threshold value, the orifice expands sufficiently to allow drug release at a required rate. For example, elastomers, such as styrene-butadiene copolymer have been suggested. Pulsatile release was achieved after lag times of 1 to 10 hrs, depending on the thickness of the barrier layer and that of semi permeable membrane. A capsule designed for implantation can deliver drug intermittently at intervals of 6 hours for 2 days.

(

3) Pulsatile system with erodible or soluble barrier coatings:

Most of the pulsatile drug delivery systems are reservoir devices coated with a barrier layer. This barrier erodes or dissolves after a specific lag period, and the drug is subsequently released rapidly from reservoir core. The lag time depends on the thickness of the coating layer.

(a) The chronotropic system: The Chronotropic system (**Fig.4**) consists of a drugcontaining core coated by hydrophilic swellable HPMC that produces lag phase.

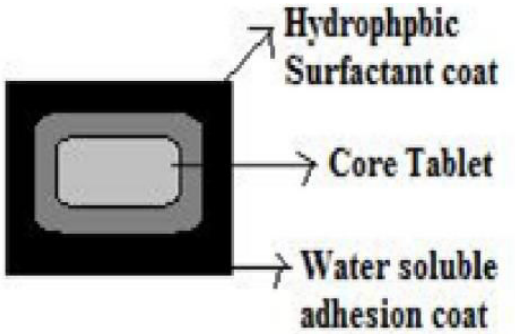

FIG.5: SCHEMATIC DIAGRAM OF DELIVERY SYSTEM WITH RUPTURABLE COATING LAYER.

(b) Compressed tablets:

Compression coating involves direct compression of both the core and the coat, averting needs for use of coating solutions. The outer tablet of the compression-coated tablet provides the initial dose, rapidly disintegrating in the stomach and the inner layer is formulated with components that are insoluble in gastric media but are released in the intestinal environment. Cellulose derivative may be used for this purpose. Compression is easy on laboratory scale. The major drawbacks of this technique are that relatively large amounts of coating materials are needed and it is difficult to position the cores correctly. Advantages of Press-coated pulsatile drug delivery systems can protect hygroscopic, light sensitive, acid labile drug, they are simple and cheap in making.

(c) Multilayered Tablets:

Two pulses can be obtained from a three layered tablet containing two drugs containing layers separated by a drug-free gellable polymeric barrier layer (**Fig 5**). This three-layered tablet is coated on three sides with impermeable ethyl cellulose, and the top portion was left uncoated. Upon contact with dissolution medium, the initial dose incorporated into the top layer was released rapidly from the non coated surface. The second pulse is obtained from the bottom layer after HPMC layer gets eroded and dissolved. The rate of gelling or dissolution of the barrier layer control the appearance of the second pulse. The gelling polymers reported include cellulose derivatives like HPMC, methyl cellulose, or polyvinyl alcohols of various molecular weights and the coating materials include ethyl cellulose, cellulose-acetate propionate, methacrylic polymers, acrylic and mehtacrylic co-polymers, and polyalcohols.

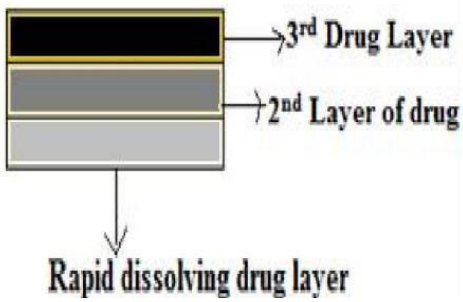

FIG. 6: MULTILAYERED TABLET

4. Multiparticulate System:

(1) Pulsatic system with rupturable coating:

Time –controlled Explosion system (TCES) **Fig. 6** Multiparticulate system where drug is coated on non-pareil sugar seeds followed by a swellable layer and an insoluble top layer coating. The swelling agents used include Superdisintegrants like sodium

carboxymethyl cellulose, sodium starch glycollate, L-hydroxypropyl cellulose and Polymers like polyvinyl acetate, polyacrylic acid, polyethylene glycol, etc. Alternatively, effervescent system comprising a mixture of tartaric acid, citric acid and sodium bicarbonate may also be used. Upon ingress of water, the swellable layer expands, resulting in rupture of film with subsequent rapid drug release. This release is independent of environmental factors like pH and drug solubility. The lag time can be varied by varying coating thickness or adding high amounts of lipophilic plasticizer in the outermost layer. A rapid release after the lag phase can be achieved with increasing concentration of osmotic agent. *In-vivo* studies of time-controlled explosion system (TCES) with an in-vitro lag time of three hours showed appearance of drug in blood after 3 hours, and maximum blood levels after 5 hours

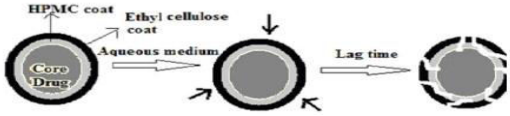

FIG.7: TIME –CONTROLLED EXPLOSION SYSTEM

(2) Osmotic based rupturable coating system:

This system is based on a combination of osmotic and swelling effects. The core contains drug, a ow bulk density solid and/or liquid lipid material (eg, mineral oil) and a disintegrant. The core is finally coated with cellulose acetate. Upon immersion in aqueous medium, water penetrates the core displacing lipid material. After the depletion of lipid material, internal pressure increases until a critical stress is reached, which results in rupture of coat. Another system is based on a capsule or tablet composed of a large number of pellets with different release pattern. Each pellet has a core that contains the therapeutic drug and a water-soluble osmotic agent. Water-permeable, water-insoluble polymer film encloses each core. A hydrophobic, water-insoluble agent that alters permeability (e.g. a fatty acid, wax, or a salt of fatty acid) is incorporated into the polymer film. The rate of water influx and drug efflux causes the film coating of each population to differ from any other pellet coating in the dosage form. The osmotic agents dissolve in the water causing the pellets to swell, thereby regulating the rate of drug diffusion. The effect of each pellet population releasing its drug content sequentially provides a series of pulses of drug from a single dosage form. The coating thickness can be varied amongst the pellets. This system was used for the delivery of antihypertensive drug, Diltiazem. The use of osmotically active agents that do not undergo swelling is also reported. These pellet cores contain drug and sodium chloride coated with semipermeable cellulose acetate polymer. This coat is selectively permeable to water and is impermeable to the drug. Sodium chloride facilitated the desired fast release of drug. In absence of sodium chloride, a sustained release of drug was achieved after lag time due to lower degree of core swelling that generated small fissures.

Pulsatile Delivery by Change in Membrane Permeability:

The permeability and water uptake of acrylic polymers with quaternary ammonium groups can be influenced by the presence of different counter-ions in the medium. Several delivery systems based on this ion exchange have been developed. Eudragit is a polymer of choice for this purpose. It typically contains positively polarized quaternary ammonium group in the polymer side chain, which is always accompanied by negative hydrochloride counter-ions. The ammonium group being hydrophilic facilitates the interaction of polymer with water, thereby changing its permeability and allowing water to permeate the active core in a controlled manner. This property is essential to achieve a precisely defined lag time. The cores were prepared using theophylline as model drug and sodium acetate. These pellets were coated using Eudragit (10% to 40% weight gain) in four different layer thicknesses. A correlation between film thickness and lag time was observed. It was found that even a small amount of sodium acetate in the pellet core had a dramatic effect on the drug permeability of the Eudragit film. After the lag time, interaction between the acetate and polymer increases the permeability of the coating so significantly that the entire active dose is liberated within a few minutes. The lag time increases with increasing thickness of the coat, but the release of the drug was found to be independent of this thickness and depended on the amount of salt present in the system.

Need for pulsatile drug delivery system:

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

Asthma:

Circadian changes are seen in normal lung function, which drops in the early morning hours. The decreased lung function is more pronounced in people with asthma**.** It is usually highest at 4 pm and lowest at 4 am. It is the 4 am when asthma is more prevalent.

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

Duodenal Ulcer:
Gastric acid secretions are highest at night. Suppression of nocturnal acid is an important factor in duodenal ulcer healing, once daily bed time dosage regimen is recommended for H2antagonists.

Cancer:
Chemotherapy may be more effective and less toxic if anticancer agents are administered keeping in mind the tumor cell cycles. This way it will be less toxic to normal tissue. Blood flowto tumors and tumor growth rate are each up to three fold greater during each daily activity phase of circadian cycle than during daily rest phase. Chronotherapy concept offers promise for improving current cancer treatment options. However chronotherapy is still uncommon, limited to only 50 cancer centers throughout world.

Diabetes:
Circadian behavior in glucose and insulin secretion in diabetes was revealed and studied. Increase in blood sugar level is found after meal

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

Neurological Disorder:
Investigation on epilepsy and convulsion demonstrate chronological rhythm. It is mentioned that brain area with highest concentration in noradrenergic nerve terminals and noradrenalin have a circadian rhythm in their content of noradrenalin.

Cardiovascular Diseases:
Angina pectoris, ventricular arrhythmia, acute myocardial infarction, sudden cardiac death, stroke, fatal pulmonary embolism, and hypertensive crisis's all are most frequent in morning as are other cardiovascular conditions. Cardiovascular events in a diurnally active person achieves peak in between 6 am to 10 pm.

Current and future developments:
The future of chrono modulated drug delivery systems are more specifically the future of delivering drugs in pulsatile manner. The prime advantage in this drug delivery is that drug is released when necessity comes. As a result chance of development of drug resistance which is seen in conventional and sustained release formulations can be reduced. Furthermore, some anticancer drugs are very toxic. These drugs give hazardous problems in conventional and sustained release therapies. Now many FDA approved chronotherapeutic drugs are available in the market. This therapy is mainly applicable where sustained action is not required and drugs are toxic.

CONCLUSION:

Rapid advancement and newer developments in the field of drug delivery have led to the formulation of the pulsatile drug delivery system, which, on one hand, can be formulated with ease and, on the other hand, provides a significant amount of therapeutic benefits. These systems deliver the drug at right time, place and amount in the patient's body. The circadian disorders generally require chronopharmacotherapy, which can be easily accomplished by pulsatile drug delivery system in a very organized manner.

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