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PULSATILE DRUG DELIVERY SYSTEM: A MECHANISTIC UPDATE

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Abstract:
Pulsatile drug delivery systems are the systems which deliver the drug according to the circadian rhythm of the body. The product follows a sigmoidal drug release profile characterized by a time period of no release (lag time) followed by a rapid and complete drug release. Thus, these systems deliver the drug at the right site of action at the right time and in the right amount, thus providing spatial and temporal delivery and increasing patient compliance. Various capsular, osmotic, single and multiple unit systems that are modulated by soluble or erodible polymer coatings, rupturable membranes are available in the market. Chronotherapeutics have been used for number of diseases like asthma, arthritis, cancer, diabetes, epilepsy, hypotension, ulcer, hypercholesterolemia etc. These are beneficial for diseases showing chronopharmacological behaviour where night time dosing is required and for drugs having high first pass effect or having site specific absorption in gastrointestinal tract or drugs having high risk of toxicity or tolerance.

Keywords: *Pulsatile, circadian rhythm, chronotherapeutics, hypercholesterolemia, chronopharmacological behaviour.*

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INTRODUCTION:

Pulsatile drug delivery refers to rapid and transient release of a certain amount of drug molecules within a short time-period immediately after a predetermined off-release period. These are the systems which deliver the drug at the right site of action at the right time and in the right amount, thus providing spatial and temporal delivery and improve patient compliance [1]. Some diseases have predictable cyclic rhythms and that the timing of medication regimens can improve outcome in selected chronic conditions [2]. Diseases which required to be formulated as pulsatile drug delivery system are: asthma, hypercholesterolemia, cancer, duodenal ulcer, arthritis, diabetes, neurological disorders, cardiovascular diseases and colonic delivery [3]. Circadium rhythm regulates many body functions in humans viz, metabolism, behaviour, physiology, sleep patterns, hormone production etc[4]. A new concept of chronopharmaceutics has emerged, wherein research is devoted to the design and evaluation of the drug delivery systems that release a therapeutic agent at a rhythm that ideally matches the biological requirement of a disease therapy[5]. "Chronotherapeutics" consists of two words Chronobiology and pharmaceutics. Chronobiology is the study of biological rhythms and their mechanisms [6]. Chronotherapeutics is the discipline concerned with delivery of drugs over a certain period of time[7].

The time between when a dosage form is placed into an aqueous environment & the time at which the active ingredient begins to get released from the dosage form is termed as lag time[8].

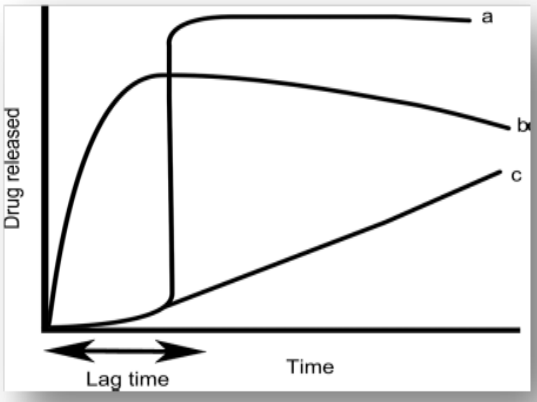

Fig 1.Drug release profile. A.Sigmoidal drug release. B.Extended release. C.Extended release after lag time.

There are 3 types of mechanical rhythms in our body. They are:

Circadian- 'Circa' means about and 'dies' means day.

Ultradian- Oscillations of shorter duration.

Infradian- Oscillations which are longer than 24 hour [9].

Advantages:-

Decreased side effects.

Improved patient compliance.

Pulse release allows multiple dosing in a single dosage form.

These systems can be utilised for many solid dosage forms like granules, microspheres, microparticles, tablets, capsules and pellets.

Site targeting allows delivery of poorly bioavailable drugs that would get destroyed in higher gastrointestinal tract environment. E.g. peptide and protein molecules.

Reduces drug dose without decrease in therapeutic effects.

Decreases drug interaction due to lower cytochrome P_{450} isoenzymes.

Increase absorption and bioavailability than conventional release drug due to its ability to release drug at target site of absorption in a burst manner [10].

Classification:-

1. Time Controlled System:-

A) Single unit (e.g.tablet or capsule).

B) Multiple units (e.g.pellets or beads).

A) SINGLE-UNIT SYSTEMS:-

a. Capsule systems.

b. Capsular systems based on osmosis.

c. Pulsatile system with erodible or soluble barrier coatings.

d. Pulsatile system with rupturable coating.

B) MULTIPLE-UNIT SYSTEMS:-

a.Pulsatile system based on rupturable coating.

b.Osmotic-Based Rupturable coating systems.

c.Pulsatile drug delivery by change in membrane permeability.

A.Single Unit Systems:

The various single unit systems have been explained as follows-

a) Capsule system with a swellable plug:

Pulsincap system:-It consists of gelatine capsule body coated with ethyl cellulose. The molded hydrogen is used to seal the contents of the drug into the capsule body. In the presence of fluids, plug developed a frustoconical shape and slowly pulled itself out of capsule at a controlled rate independent of nature and ph of the medium giving a rapid bulk release[11].

A rapid release is ensured by inclusion of effervescent agents or disintegrants. The plug consists of insoluble but permeable and swellable polymers(polymethacrylates), erodible compressed polymers (hydroxypropylmethyl cellulose, polyvinyl alcohol), congealed molted polymers(glyceryl monooleate), and enzymatically controlled erodible polymer(pectin).

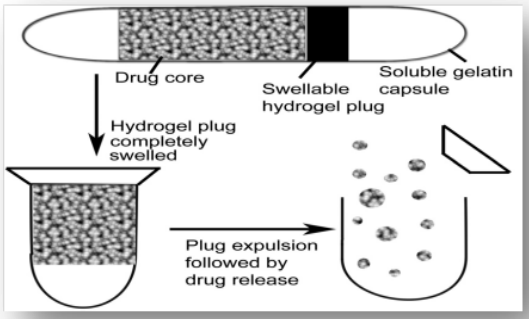

Fig. 2. Pulsincap System

b)Capsule system based on osmosis:

The basic appliance in the osmotic system is a capsule enclosed with a semipermeable membrane. An insoluble plug, osmotically active agent, and the therapeutically active agent is present inside the capsule body. When capsule comes in contact with body fluids, the semipermeable membrane allows the entry of water and developed a pressure, due to this the insoluble plug is expelled after some lag time[12].

PORT system consists of semipermeable body divided into compartment by a slidable separator. The internal body contained two compartments separated by non-swellable slider plug. The upper water had a immediate release while the lower compartment compartment had an active therapeutic agent with an osmotically active agent[13].

As a water diffuses into the capsule body through the semipermeable membrane, osmotic pressure is developed

because of solubilisation of osmotically active agent.

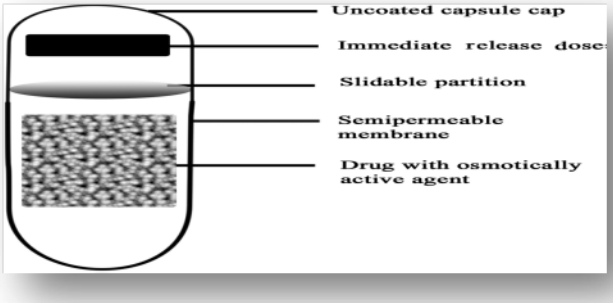

Fig 3: The PORT system.

c) Pulsatile system with erodible or soluble barrier coating:

Some delivery systems are reservoir devices coated with a barrier layer. After a specific lag period, this barrier erodes and dissolves, and the drug is released rapidly. The lag time depends on the thickness of the coating layer. This coat erodes or emulsifies in an aqueous environment. These systems are used for water soluble drugs. However, lipid based systems may have high in-vivo variability [14,15].

d) Pulsatile system with rupturable coating:

These systems depend on the disintegration of the coating for the release of drug. Effervescent excipients, swelling agents or osmotic pressure was necessary for the rupture of the coating. Mixture of citric acid and sodium bicarbonate with ethyl cellulose can be used. The release of drug after rupture of the coating depends on the carbon dioxide developed after penetration of water into the core [16].

B.Multiple Systems:

Multiple systems (e.g. pellets, beads) have various advantages over single unit systems. These include reproducibility, no risk of dose dumping and short gastric residence time.

a) Pulsatile system based on rupturable coating:

In this system, drug is coated on non-pareil sugar seeds having a swellable layer and an insoluble top layer. The swelling agents used are superdisintegrant like sodiumcarboxymethyl cellulose, sodium starch glycollate, polymers like polyvinyl acetate, polyacrylic acid , polyethylene glycolate. An effervescent system consisting of a mixture of tartaric acid and sodium bicarbonate may also be used as an alternative [17,18].

b) Osmotic-based rupturable coating systems:

This system is a combination of osmotic and swelling effects. In it, the core containing the drug, a disintegrating and a low bulk density solid or liquid lipid material (e.g.mineral oil) was prepared. Core was coated with cellulose acetate upon immersion in aqueous medium, water penetrates the core displacing lipid material. The internal pressure increases until the critical stress is reached, after the depletion of lipid material, resulting in rupture of coating [19].

c) Pulsatile drug delivery by change in membrane permeability:

The permeability and water uptake of acrylic polymers with quaternary ammonium groups can be influenced by presence of different counter-ions in the medium. A polymer used for this purpose is Eudragit RS 30D. It consists of positively polarized quaternary ammonium group in the polymer side chain, accompanied by negative hydrochloride counter ions. The ammonium group which is hydrophilic facilitates the interaction of polymer with water, thereby changing its permeability and allowing water to permeate the active core in a controlled manner [20].

2. Internally Stimuli Induced System:-

A) Temp. Induced pulsatile release:

a) Thermoresponsive hydro gel systems.

b) Thermoresponsive polymeric micelle systems.

B) Chemical stimuli induced pulsatile release:

a) Glucose-responsive insulin release devices.

b) Ph sensitive drug delivery system.
c) Inflammation-induced pulsatile release.
d) Drug release from intelligent gels responding to antibody conc.

3. Externally Regulated System:
a) Ultrasound induced release.
b) Magnet induced release.
c) Electric field induced release.
d) Light induced release.

2. Internally Stimuli Induced-
Systems can be explained as follows**;**

A) Temp. Induced pulsatile release:
Temperature is the most widely applied signal for pulsatile drug delivery.

a) **Thermo responsive hydro gel systems:** When temp. changes, hydrogel undergo reversible volume changes. These are known as thermosensitive gels. At a transition temp., these gels shrink which is referred to as LCST(lower critical sol. temp.)(21,22,23).
b) **Thermo responsive polymeric micelle systems:** When end functionalised PIPAAm combine with hydrophobic polymers like BMA poly(buty methacrylate), PST(postyrene), block polymers are formed. Below PIPAAm transition temp., bnlock copolymers formed micelle structure in aqueous solution. The release of drug takes place when polymer undergo swelling or deswelling phase (21, 22, 23).

B) Chemical Stimuli Induced Pulsatile Release:
a) Glucose- responsive insulin release devices: It has been developed to change the conc. of glucose in the blood. These showed a glucose-responsive, sol-gel phase transition. These devices have ph sensitive hydro gels which contain glucose oxidase immobilized in the hydrogel. e.g. of ph sensitive polymers:-N,N.dimethyl aminoethyl methacrylate, Chitosan(21,24,25,26).

b) pH sensitive drug delivery system: These system has two main components. One has a immediate release and another for pulsed release which releases the drug in response to change in ph. At specific location, the desired drug release can be achieved by selecting the appropriate ph dependent polymers (21,24,25,26).

c) Inflammation-induced Pulsatile Release: At the injured sites, any physical or chemical stresssuch as injury, fracture etc. cause inflammation. The inflamed responsive cells produce hydroxyl radicals. Hyaluronic acid is used which is degraded by hyaluronidase or free radicals. So, for the treatment of inflammatory diseases like rheumatoid arthritis, anti-inflammatory drug incorporated HA gels was use as new implantable drug delivery systems(23,24,27,28,29)

d) Drug release from intelligent gels responding to antibody conc.: Various kinds of bioactive compounds exist in the human body. To detect the change in conc. of these bioactive compounds, recently novel gels are developed to alter their swelling/deswelling characteristics. When utilization of the different in association constants takes place between polymerized antibodies & naturally derived antibodies towards specific antigens, reversible gel swelling/deswelling & drug permeation changes occur.

3. Externally Regulated System:
a) Ultrasound induced release: In this system for the improvement of drug permeation through biological barriers such as skin, lungs, intestinal wall and blood vessels, ultrasound is used as an enhancer (30,31,21,32).
b) Magnetic induced release: In this oscillating magnet is used to regulate the delivery of drug from polymer matrix. Materials like iron, magnetite, cobalt, nickel and steel can be incorporated to experience a magnetic field. Magnetic steel beads are engrafted in an ethylene & vinyl acetate(EVAc) copolymer matrix that is loaded with bovine serum albumin as a model drug(30,31,21,32).
c) Electric field induced release: Magnetically regulated system contains magnetic beads in the implant. In it, polyelectrolytes (polymers that contain high concentration of ionisable group) & are thus ph-responsive as well as electroresponsive (30, 31, 21, 15).
d) Light induced release: To regulate drug delivery, the interaction between light and material can be used. Interaction takes place by combining a material that absorb light at a desired wavelength & a material that uses energy from the absorbed light to regulate drug delivery(30,32,23,33).

Evaluation of Core Tablets:
The core tablets are evaluated for the following parameters-:

1) Tablet hardness.
2) Weight Variation.
3) Friability.
4) Tablet thickness.
5) Disintegration time.
6) In-vitro dissolution studies.
7) Assay.
8) Stability testing.

1) Tablet hardness:-
The resistance of tablets to shipping or breakage under conditions of storage, transportation and handling before usage depends upon its resistance. It can be checked by using Monsanto hardness tester. Hardness of 3 determinations is usually recorded.

2) Weight variation:-
The USP weight variation test is done by weighing 20 tablets individually, calculating the average weight. The tablets meet the USP specification

when not more than two tablets are outside the percentage limit. Weight variation limits are as follows:-

Table No. 1. Wt. Variation limits.

S. No.	Avg. Wt. of tablet	Max. % difference allowed
1.	130 or less	10
2.	130-324	7.5
3.	324<	5

3) Friability:-

It refers to loss in weight of tablets in the containers due to removal of fines from the tablet surface. 20 tablets are weighed and the initial weight of these tablets is recorded. The weighed tablets are then placed in Roche friabilator and rotated at the speed of 25 rpm for 100 revolutions.

4) Tablet thickness:-

It can be measured by using Vernier Calliper. It is determined by checking the thickness of 10 tablets of each formulation.

5) Disintegration time:-

It is carried out in USP disintegration test apparatus. It consists of glass tubes which are 3 inches long, open at top. To test the disintegration time of tablets, one tablet was placed in each tube and the basket rack was positioned in a 1 litre beaker containing buffer solution at 37±1°C. The time taken for the complete disintegration of the tablets is noted.

6) *In-vitro* dissolution testing:-

USP type apparatus is used for dissolution testing. For the testing, dissolution medium used for ph 1.2,6.8,7.4 phosphate buffer. Compression coated tablet is placed in ph 1.2 phosphate buffer for 2 hours due to gastric emptying time of 2 hours. 5ml sample are pipette out at specific interval (1 hour). Then that medium of ph 1.2 is replaced by ph 6.8 phosphate buffer and testing carried out for 3 hours because of intestinal emptying time. After that the medium of ph 6.8 is replaced by 7.4 phosphate buffer and it is carried out for 12 hours and drug release is carried out for 12 hours and drug release was checked in particular medium by using UV at 246nm. Dissolution test is performed and results are recorded.

7) Assay of tablets:-

20 tablets are weighed and finely powdered. Powder equivalent to the 2.5 mg is taken in 25ml of volumetric flask. 5 ml of mixed hydrotropic solution containing 45% urea and 8% Na citrate is added. Shake for 10 minute. Make up the volume upto the mark. Filter extract, dilute it with distilled water. Take absorbance at 244.8mm against reagent black and drug content is calculated.

8) Stability testing:-

It is carried according to ICH to determine the drug formulation stability. Formulation is sealed in al packaging laminated with polythene. Samples are kept at 40°C and 75%RH FOR 3 months. After 3 months, this tablet is evaluated for stability by using IR for that firstly the individual IR of Eudragit, guar gum, budesonide are taken and then IR of compression coated tablet in mortar with the help of pestle and results are concluded from the IR graph, and also the DSC is performed for checking the stability of compound [34,35,36].

Market Formulations Based On Pulsatile Drug Delivery:

OROS technology (Osmotic-controlled Release Oral delivery System):

This technology uses osmotic agents to provide preprogrammed drug delivery to the gastrointestinal tract. This is used to design a novel antihypertensive product.

Available marketed products:

Alpress LP (Prazosin)

Covera-HS (Verapamil)

Procardia XL (Nifedipine)

CODAS technology (Chronotherapeutic oral drug absorption system):

It is multiparticulate system, dosed at bed time that delays drug release for 4-5 hours.

Marketed product:

Veralan PM XL Capsule API

Verapamil HCl

CEFORM technology:

It is used for development of microspheres of uniform size and shape. It is based on 'melt spinning' in which biodegradable polymer or bioactive agents is subjected to combination of temp., mechanical forces, flow & flow rates during processing.

DIFFUCAPS technology:

In this, unit dosage form like capsule is prepared. It consists of drug which contain particles(beads, pellets, granules etc). The drug core consist of inert particle or alkaline buffer crystal(cellulose ethers) which is coated with hydrophilic API containing film forming agents like HPMC, PVC etc. It has been used in formulating Innopran XL containing Propranol for hypertension.

Marketed product:

Innopran XL Tablets Verapamil HCl

Zofran Tablets Ondansetron HCl dihydrate

PULSYS technology:

It is used to develop chronotherapeutic system for amoxicillin.

TIMER technology:

It uses two polymers xanthun gum and locust bean gum which is mixed with dextrose. In the presence of water, these form a strong binding gel due to physical interaction between these components. Release of drug is controlled by rate of water penetration from gastrointestinal tract to the gum matrix, which expands to form a gel and release active drug substance. It is used in development of oral, controlled release.

SODAS (Spheroidal Oral drug absorption system):
This technology produce a controlled release beads.
PRODAS(Programmable Oral Drug Absorption System):
It is a combination of both multiparticulate $hydrophilic matrix tablet in which various no. of minitablets gattered in a hard gelatine capsule(37-40).
RECENT ADVANCES IN THE PULSATILE DRUG DELIVERY:
ACCU-BREAK Technology:
In this, tablet contain a controlled release $ immediate release tablet[38].
TMDS Technology:
It gives a control release rate of multiple ingredients within a single tablet[38].
GEOCLOCK Technology:
In this, press coated tablets are used, in which active drug surrounded by a tablet layer which contain a mixture of hydrophobic wax $ brittle material. e.g. 20 DOTRA used in Rheumatoid Arthritis[38].
DUREDAS Technology(Dual Release Drug Absorption System):
In this, bilayer tablets are used. One layer give immediate release while second layer give sustained release[39].
KV/24:In this, release of drug occurs when one or more drug compounds remain encapsulated in a pre-determined fashion. The drug can be combined in a 2 ways. One with neutral core, another into the coating press 20[40].
INNOHERB:
In this, pellets are coated inside the capsule[40]
IPDAS(Intestinal Protective Drug Absorption System):
In this controlled release tablets, the beads with high density drugs are compressed. The release is controlled by the nature of drug which contain bead matrix or its semi-permeable membrane coating[38,39,40,41].

CONCLUSION:

It can be concluded that pulsatile drug delivery systems offer a solution for delivery of drugs exhibiting chronopharmacologic behaviour, extensive first pass metabolism, night-time dosing or absorption window in GIT.
A variety of systems based on single or multiple units have been developed for pulsatile release of drug. One major challenge will be to obtain a better understanding of the biological environment on the release performance of pulsatile delivery systems in order to develop simple systems based on approved excipients with a good in vitro-in vivo correlation.
Identification of a rhythmic marker by choosing chronopharmacotherapy offers more benefits for both local and systemic effects by reducing unwanted side effects. The main advantage of colon targetting combined with chronopharmacotherapy is that it not only protects the drug from acidic environment by reducing side effects but also makes possible the availability of proteins and peptides based drugs to the target site in their intact form and also provides desired release at target site by means of pulsatile drug delivery systems especially in circadian rhythm based on diseases.

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