Review on: Pulsatile Drug Delivery System

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Abstract **- Pulsatile drug delivery systems (PDDS) are acquiring a lot of interest as they deliver the medication at the right place at the right time and in the right amount, subsequently giving spatial and transient delivery and increasing patient consistency. A pulse must be planned so that a complete and rapid medication release is accomplished after the lag time. A different system such as capsular system, osmotic system, single- and multiple unit system dependent on the utilization of soluble or erodible polymer coating, and the utilization of rupturable films has been managed in the article. Pulsatile drug delivery is one such system that, by delivering drug at the right time, right place, and in right amounts, holds good promises of benefit to the patients suffering from Peptic ulcer, Asthma, Cardiovascular disease, Diabetes mellitus and Hypercholesterolemia etc.**

Index Terms **- Pulsatile drug delivery system, Single unit pulsatile systems, Pulsatile system based on Osmosis, Lag time, circadian rhythm.**

INTRODUCTION

The oral route of drug delivery is typically considered the favoured and the most having the highest degree of patient compliance because of user-friendly means of drug administration.1 Traditionally, drug delivery systems have focused on constant/sustained drug output with the objective to optimize drug efficacy and to reduce adverse effects. A reduced dosing frequency and improved patient compliance.2Pulsatile systems are gaining a lot of interest as they 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. The release of the drug as a pulse after a lag time has to be designed in such a way that a complete and rapid drug release follows the lag time. These systems are designed according to the circadian rhythm of the body. The principal rationale for the use of pulsatile release is for the drugs where a constant drug release, i.e., a zero-order release is not desired.3

Pulsatile Drug Delivery Systems: 4-6

A Pulsatile drug delivery system delivers drug in rapid and burst manner within a short time period immediately after a programmable lag phase. There are many situations where drug is needed to be released immediately (after bursting the delaying film coat) at specific site. These situations, therefore, compel designing a delayed fast release system. These systems are mainly appropriate for drugs that are metabolized to pharmacological active compounds, drugs which have long in vivo half-life showing an inherently prolonged duration of action, drugs with very short in vivo half-life which require a prohibitively large amount of active ingredients in dosage form, drugs which are required in large doses for therapeutic effect and drugs which are required in very low dose. Additionally, a delayed burst release can also be utilized for enhancing absorption, reducing side effects, increasing and decreasing dose

BENEFIT OF PDDS

There are numerous benefits of the pulsatile measurement structure over regular dose structure.

1. Increase the absorption and bioavailability than conventional immediate release or sustained release drugs because of their capacity to deliver the medication in a burst way, at the objective site of assimilation.
2. Site targeting permits the delivery of poorly bioavailable medications that would get destroyed in a higher GIT climate, for example, (peptide and protein molecule).

3. Lessens the dose of the medication without decreasing the therapeutic effect.
4. Decreasing the adverse effect.
5. Decrease drug interaction because of the lower cytochrome P450isoenzymes.
6. Decrease food impact (change happening in bioavailability of medication when given with food).
7. Improved patients' consistency.
8. Chronotherapy modified delayed discharge gives an ideal treatment of the disease.
9. Pulse discharge allows various dosing in a single dosage form.
10. Broadened daytime or night-time activity.7
11. Lower day-by-day expenses to the patient because fewer dosage units are needed by the patient in treatment.
12. Medication adjusts to suit circadian rhythms of the body.
13. Shields mucosa from aggravating medications.
14. Medication loss is prevented by the first-pass metabolism.
15. No danger of dose dumping.
16. Because of its ability to deliver the medication in a burst way, it will increase absorption and bioavailability at the target site of absorption Avoid biological tolerance.
17. Expectable, reproducible, and little gastric dwelling period.
18. Adaptability in drug delivery system designing.8-10
19. They give constant medication levels at the site of activity and prevent the peak-valley changes.11

DRAWBACK OF PDDS

1. Low drug loading capacity and fragmented arrival of the drug.
2. Greater expense of production.
3. A large number of process variables.
4. Absence of assembling reproducibility and viability.

Drug release profiles from pulsatile drug delivery system

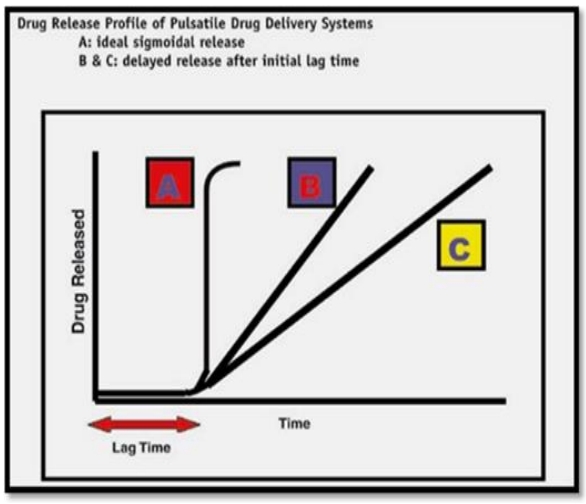

Fig.1 Drug release profiles from pulsatile drug delivery system

Classification of Pulsatile Drug Delivery Systems: 12-17

Time controlled pulsatile drug delivery:

(A) Single unit pulsatile systems:

a) Capsule based systems: Pulisin cap 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 rug is released Pulsin cap (Fig.2) was developed by R. P. Scherer International Corporation, Michigan, US, and is one such system that comprises of a waterinsoluble 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.

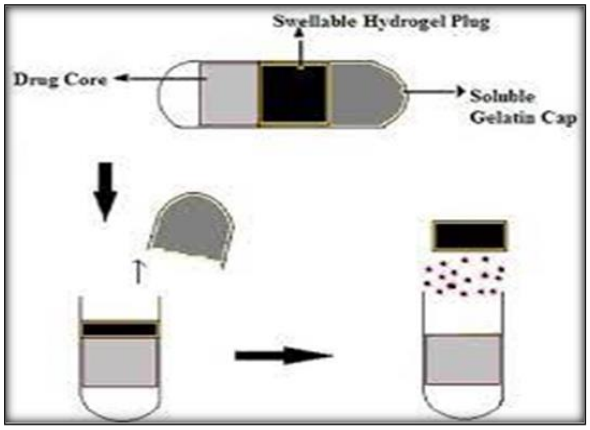

Fig.2 Design of pulsin cap system.

b) Pulsatile system based on Osmosis 18

Osmotic structure contains tablet covered through the semipermeable film. Exclusive the case here was an mysterious attachment comprising of osmotically dynamic specialist and the medication content. At the point when the case interacts with the disintegration liquid, the semipermeable layer permitted the passage of water in to the capsule due to presence of small pore, which causes pressure to be developed & the insoluble attachment ousted after a slack time. Such a framework was used to convey methylphenidate utilized in the treatment of consideration shortage hyper movement issue as the pulsatile port system.19-20

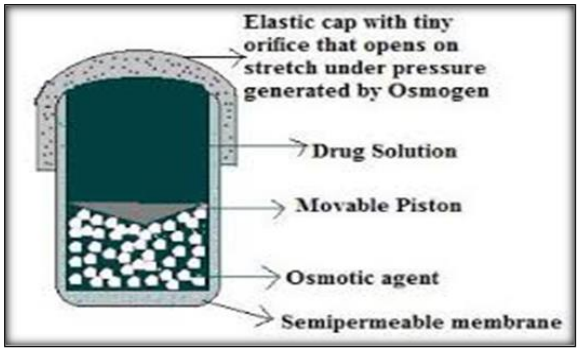

Fig.3 Schematic diagram of osmosis system

c) Capsule shaped system providing through release regulatory plug 21

Single - unit frameworks are created in case structure. The slack time is controlled as an attachment, which gets drove missing by growing or disintegration, & the medication is discharged as a heartbeat from the insoluble container structure the case body. This dose structure comprises of an mysterious container body comprising a medication and swellable & degradable fittings through of elements, for example, hydrophilic polymers or lipids. The slack time can be constrained by controlling the measurement and the situation of the attachment.

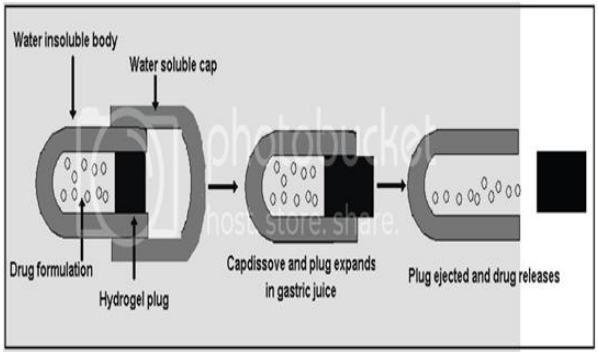

Fig.4 Schematic drawing of release of drug from tablet

d) Delivery systems through rupturable covering layer 22

This system mainly subject to the breaking down of the covering for the arrival of medication. The weight fundamental for the break of the covering can be accomplished by the expanding, disintegrants, bubbly and so on. The slack time can be influenced by water saturation and mechanical opposition of the film. Eg: Buflomedi Hcl is used for treatment of peripheral.

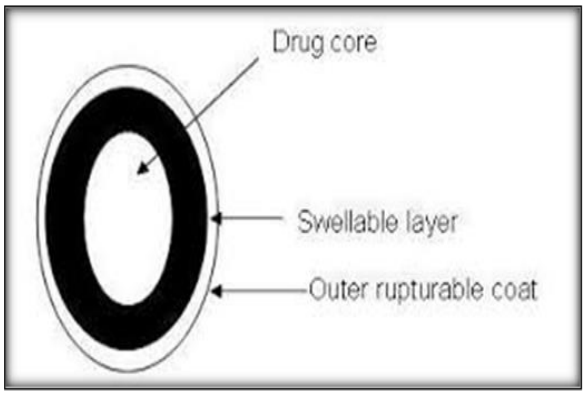

Fig.5 Schematic diagram of drug delivery through rupturable covering layer

e) Delivery system through erodible covering coatings 22

In this system, the centre covering drug is covered through the solvent or erodible polymer as external covering and the medication discharge is constrained by the disintegration or disintegration of the external coat. Time subordinate arrival of the medication can be gotten by upgrading the thickness of the external covering as appeared in fig6.

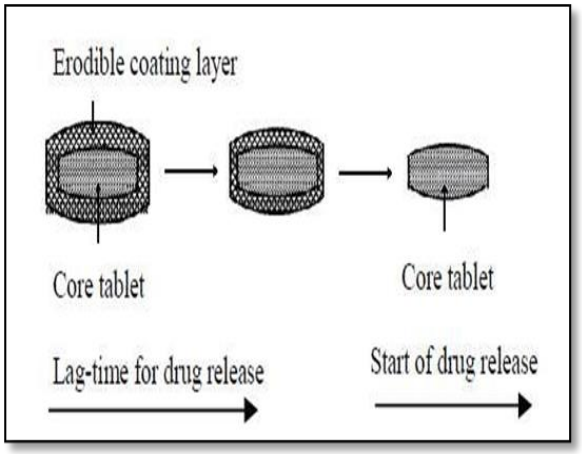

Fig.6 Schematic diagram of drug delivery through erodible covering layer

B. Stimuli brought pulsatile release system 23
In this method, arrival of the medication after incitement by any organic factor like high temperature, pH or any additional chemical agents 24.

This method further categorized as six types

a. Temperature tempted systems
b. Thermo receptive hydrogel and polymer systems
c. Chemical stimuli induced pulsatile system
d. Inflammation - induced pulsatile statement
e. Drug release from intelligent gels retorting to antibody absorption
f. pH sensitive drug delivery system

a. Temperature induced systems:
Temperature instigated frameworks uses different polymer properties, for example, thermally reversible curl/globule progress of polymer particles growing difference in systems, glass change and translucent liquefying 25.

b. Thermo receptive hydrogel & polymer systems
In this system the polymer experiences growing or de-swelling stage in light of the high temperature which tweak tranquilize discharge in distended state27-28.

c. Chemical improvements instigated pulsatile system 27
In a glucose-rich atmosphere, such as the blood level later a meal, the oxidation will stay occurred which changes glucose to gluconic acid by glucose oxidase acts as a catalyst and reduces the pH to 5.8. This pH alteration incorporates growing of the polymer which brings about insulin discharge. Insulin by excellence of its activity lessens blood glucose smooth & which thus gluconic corrosive equal likewise diminishes & framework goes to the deswelling method subsequently diminishing the insulin discharge.

d. Inflammation - encouraged pulsatile relief
During irritation, hydroxyl free radicals are delivered from the phones. The Corruption of hydroxyl free radicals happens due to infusing of hyaluronic corrosive gel at the incendiary locales. Along these lines, it is conceivable to pleasure patients through incendiary infections like rheumatoid joint pain; utilizing calming drug fused Hyaluronic Corrosive gels as implantable drug delivery systems26.

e. Drug release after insightful salves reacting to antibody absorption
There are immense number of bioactive mixes exists in the body. Presently a day, unique gels stayed created which reacted to the adjustment in convergence of bioactive mixes to modify their growing/deswelling qualities. Extraordinary consideration was assumed to antigen-immunizer compound development as the cross-connecting units in the gel, since such collaboration is unmistakable. Using the distinction in affiliation consistent's between polymerised antibodies and normally determined antibodies towards explicit antigens, revocable gel growing/deswelling and sedate pervasion deviations happens.31

f. pH sensitive drug delivery system
In this framework, it contains two segments. The first is quick discharge type and the other one is beat discharge type which discharges the medication because of progress in pH .32

g. On the exterior controlled systems
In this method, drug relief is planned by peripheral incentives similar magnetism, ultrasound, electrical influence & irradiation in order to release the drug in a pulsatile method.33

NEED OF PULSATILE DRUG DELIVERY

Pulsatile drug conveyance is fundamental when,

1. Body rhythm follows circadian rhythms.
2. Circadian rhythm is modified by the hormone-like rennin, aldosterone, cortisol, and so forth.
3. Rhythm variety is found in acid secretion in the stomach, gastric purging, and GI blood transfusion.
4. Diseases such as bronchial asthma, myocardial localized necrosis, angina pectoris, rheumatic infection, ulcer, and hypertension show time reliance.
5. Lag time is essential for the medications that go through degradation in gastric acidic medium.
6. Medications should be delivered to the distal part of GIT like a colon.
7. Medications undergo broad first-pass metabolism. 34

Table 1: Diseases required pulsatile drug delivery

Disease	Chronological behaviour	Drugs Used
Peptic ulcer	Acid secretion is high in the afternoon and at night	H2 blockers
Asthma	Precipitation of attacks during the night or at early morning hour	β2agonist, antihistaminic
Cardiovascular Disease	BP is at the lowest during sleep cycle and rises steeply during the early morning awakening days.	Nitro-glycerine, calcium channel blocker, and ACE inhibitors
Diabetes mellitus	Increase in blood sugar level after meal	Sulfonylurea, insulin, and biguanid
Hypercholesterolemia	Cholesterol synthesis is generally higher during the night than during daytime	HMG CoA reductase inhibitors

Recent advances in the pulsatile drug Delivery:

Nowadays pulsatile drug delivery systems are gaining importance in various disease conditions specifically in diabetes where dosing is required at different time points. Among these systems, multi-particulate systems (e.g., pellets) offer various advantages over single unit which include no risk of dose dumping, flexibility of blending them with different release patterns, as well as short and reproducible gastric residence time. Multi particulate systems consists pellets of different release profile which can be of any type like time dependent, pH dependent, micro flora activated system as discussed in the previous sections. Site and time specific oral drug delivery have recently been of great interest in pharmaceutical field to achieve improved therapeutic efficacy. Gastroretentive drug delivery system is an approach to prolong gastric residence time, thereby targeting site-specific drug release in upper gastrointestinal (GI) tract. Floating drug delivery system (FDDS) and bio adhesive drug delivery are widely used techniques for gastro retention. Low density porous multi particulate systems have been used by researchers for formulation of FDDS.35

CONCLUSIONS

Presently, oral delivery of drug is still by far the most preferable route of drug delivery due to the ease of administration, patient compliance and flexibility in its formulations. Generally, sustained and controlled-release products provide a desired therapeutic effect, but fall short of diseases following biological rhythms. There is a need for new delivery systems that can provide increased therapeutic benefits to the patients. Pulsatile drug delivery is one such system that, by delivering drug at the right time, right place, and in right amounts, holds good promises of benefit to the patients suffering from Peptic ulcer, Asthma, Cardiovascular disease, Diabetes mellitus and Hypercholesterolemia etc.

ABBREVIATION

PDDS - Pulsatile Drug Delivery System
GIT – Gastrointestinal Tract
HMG – Human Menopausal Gonadotropin
CoA – Coarctation of aorta
ACE - Angiotensin converting enzyme
FDDS – Floating Drug delivery System

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