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A Review on Pulsatile Drug Delivery System

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ABSTRACT:
Pharmaceutical technology is drastically developing to enhance the efficacy and safety of drug therapy. Pulsatile delivery systems, in turn, gained attraction for their ability to deliver the right drug amount to the right body site, at the right time which is advantageous over conventional dosage forms. Their use is associated with increased patient compliance and allows on-demand drug delivery as well as customizable therapy. Recent technologies have been implemented to further develop pulsatile delivery systems for more precise determination of the dosage timing and duration as well as the location of drug release. Great interests are directed towards externally regulated pulsatile release systems which will be the focus of this review. The recent advances will be highlighted in remotely controlled delivery systems. This includes electro responsive, light-responsive, ultrasound responsive, and magnetically induced pulsatile systems as well as wirelessly controlled implantable systems. The current status of these technologies will be discussed as well as the recent investigations and future applications.

Key words: Light responsive, magnetic, pulsatile delivery, remotely controlled, ultrasound, wireless.

DEFINITION:

Pulsatile drug delivery is defined as the rapid and transient release of certain amount of molecules within a short time period immediately after a predetermined off-released period, i.e., lag time, or these systems have a peculiar mechanism of delivering the drug rapidly and completely after a lag time, i.e., a period of no drug release. Such a release pattern is known as pulsatile release.

I. INTRODUCTION:

Oral drug delivery systems constitute the largest part of delivery systems in being widely distributed in the pharmaceutical market with conventional dosage forms formulated for immediate drug release and complete systemic absorption. Therefore, their administration must be repetitive to attain and maintain the drug level within the required therapeutic range. Limitations to this approach include fluctuating plasma drug levels and poor patient compliance arising from inconvenience and discomfort.Different modified delivery systems were later developed to provide a controlled drug release rate over a prolonged time period, and for localization of the drug action by spatial placement. However, in some medical conditions, controlled drug delivery is not the best choice because drug release is not needed during the early periods after dose administration. Recently, pulsatile drug delivery systems (PDDS) are gaining a growing interest by researchers. PDDS are defined as drug delivery systems able to provide one or more immediate drug release pulses at a specific time or site, after a programmable lag phase.PDDS deliver drugs at the precise time, to the target site, in the right amounts, providing maximum efficacy and benefits to the patients. Drug release from PDDS could be in an immediate or extended form.As for immediate release, PDDS exhibit rapid and transitory drug release within a short time-period instantly after a predetermined release-free period.

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CLASSIFICATION:

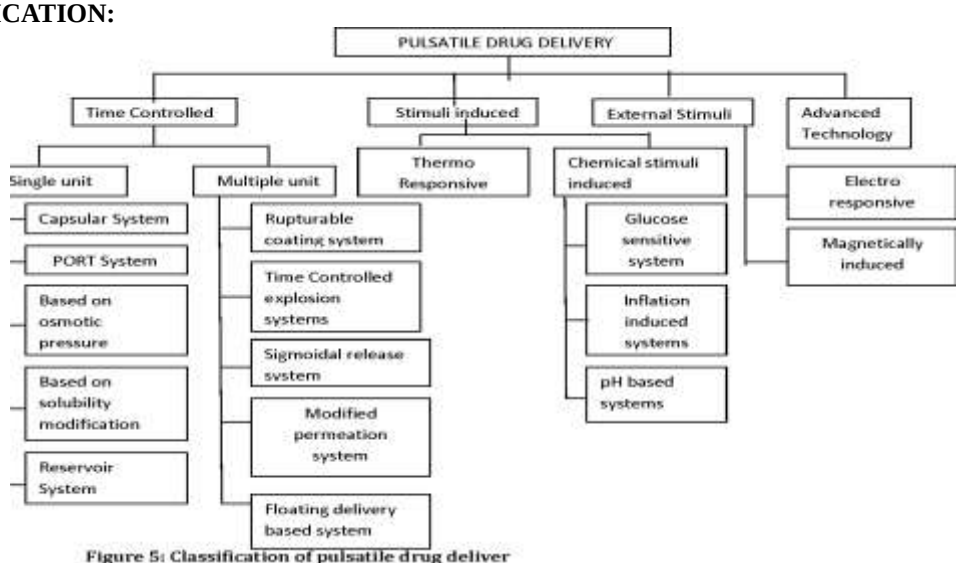

Figure 5: Classification of pulsatile drug deliver

METHODOLOGIES FOR PULSATILE DRUG DELIVERY:

Methodologies for the pulsatile drug delivery system can be broadly classified into three classes;

1. Time controlled
2. Stimuli induced
3. External regulated

1) Time controlled pulsatile release system

In time controlled drug delivery systems pulsatile release is obtained after a specific time interval in order to mimic the circadian rhythm. Such type of pulsatile drug delivery system contains two components: one is of immediate release type and other one is a pulsed release type. Various methodologies that can be used for time controlled pulsatile release systems are following:-

Delivery systems with rupturable coating layer.These systems consist of an outer release controlling water insoluble but permeable coating subject to mechanically induced rupture phenomenon. Recently different systems based on hard gelatin capsules and tablet core were described, all coated by inner swellable and outerrutpurable layer. The film rupture may be attained by including swelling, osmotic effervescent additives in the reservoir. By optimizing the system, drug release can be obtained at specific time interval.

In such systems the drug release is controlled by the dissolution or erosion of the outer coat which is applied on the core containing drug. Time dependent release of the active ingredient can be obtained by optimizing the thickness of the outer coat.

2) Stimuli induced pulsatile systems:

In these systems there is release of the drug after stimulation by any biological factor like temperature, or any other chemical stimuli. These systems are further classified as: Temperature induced systems Thermo-responsive hydrogel systems have been developed for pulsatile release. In these systems the polymer undergoes swelling or deswelling phase in response to the temperature which modulate drug release in swollen state. Y.H. Bae et al developed indomethacin pulsatile release pattern in the temperature ranges between 200C and 300C by using reversible swelling properties of copolymers of N-isopropylacrylamide and butyrylacrylamide.

➢ **Chemical stimuli induced Pulsatile system Glucose-responsive release devices**

In case of diabetes mellitus there is insulin rhythmic increase in the levels of glucose in the body requiring injection of the insulin at proper time. Several systems have been developed which are able to respond to changes in glucose concentration. One such system includes pH sensitive hydrogel containing glucose oxidase immobilized in the hydrogel. When glucose concentration in the blood increases glucose oxidase converts glucose into gluconic acid which changes the pH of the system. This pH change induces swelling of the polymer which results in insulin release. Insulin by virtue of its action reduces blood glucose level and consequently gluconic acid level also gets decreased and system turns to the deswelling mode thereby decreasing

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the insulin release. Examples of the pH sensitive polymers includes N,Ndimethylaminoethyl methacrylate, chitosan, polyol etc.

➢ **pH sensitive drug delivery system**

Such type of pulsatile drug delivery system contains two components one is of immediate release type and other one is pulsed release which releases the drug in response to change in pH. In case of pH dependent system advantage has been taken of the fact that there exists different pH environment at different parts of the gastrointestinal tract. By selecting the pH dependent polymers drug release at specific location can be obtained. Examples of pH dependent polymers includes cellulose acetate phthalate, polyacrylates, sodium carboxymethylcellulose. These polymers are used as enteric coating materials so as to provide release of drug in the small intestine.

3) Externally regulated systems

For releasing the drug in a pulsatile manner, another way can be the externally regulated systems in which drug release is programmed by external stimuli like magnetism, ultrasound, electrical effect and irradiation. Magnetically regulated system contain magnetic beads in the implant. On application of the magnetic field, drug release occurs because of magnetic beads. Saslawski et al. developed different formulation for in vitro magnetically triggered delivery of insulin based on alginate spheres. In case of ultrasonically modulated systems, ultrasonic waves causes the erosion of the polymeric matrix thereby modulating drug release. Evaluated the effect of ultrasound (1 MHz) on the release rates of bovine insulin from ethylenevinyl alcohol copolymer matrices and reservoir-type drug delivery systems in which they found sharp drop in blood glucose levels after application of ultrasonic waves.

TECHNOLOGIES IN PULSATILE DRUG DELIVERY SYSTEMS :

1. **Pulsincap Technology**: The Pulsincap system consists of a non-breakable half-case body with open end type, attached with a hydrogel plug, and covered with a water-dissolving cap. So, the entire capsule is covered with an enteric polymer used to avoid gastric emptying. When the capsule interacts with the dissolution fluid medium, it shows swelling property nature after the lag time period so the attachment propels to outside and releases the drug quickly.
2. **OROS Proprietary name**: Chronset The delivery system delivers the drug reproducibly based on the time or site-specific model in the GIT. It is completely based on the Osmosis model, in which the tablet containing the drug is present in the form of a reservoir enclosed by the semipermeable membrane with a laser-drilled orifice to deliver the drug. The bilayer and trilayer tablet systems consist of two layers with drug and osmotically active agents. When contact with the GI fluid the osmotically active agent generates the pressure and pushes the drug layer and releases of a drug through an orifice.
3. **IPDAS36:** It is another type of oral approach system of medication used for GI aggravation medications like NSAID category. So, this type of innovation is completely based on multiparticulate systems, in which high thickness/density-controlled discharge dots/beads are compacted into the tablet form. After ingestion of the IPDAS tablet, the rapid disintegration of the tablet, scatter globules containing the drug in the stomach, passes through the duodenum along with the GI tract in a continuous and controlled release manner. The drug release is based on the process of diffusion through a layer of polymer or micro matrix system of drug-polymer formation in the extruded multiparticulate system.
4. **CEFORM**: It consists of a uniform size and shape containing spherical microspheres with 150-180mm with high drug based on the process of melt spinning method in which the biodegradable polymer with combination to temperature, mechanical type of force, thermal gradients and flow of rate during the process. So, the obtained microspheres are used in a number of dosage forms like Capsules, tablets, suspensions, and effervescent-type tablets. The coated microspheres with enteric polymers are used for controlled release.
5. **DIFFUCAPS**:The capsule-based system with single or more drug particles includes beads, pellets and granules. Each particle expresses the preprogrammed release pattern with rapid /sustained action with /without a lag time. Diffucap system comprises a number of layers with drug release-controlling polymers

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and Excipients. The particles contain the organic acid/alkaline buffer, which is used to control the drug solubility.

6. **EGALET:** Delayed release type of system with an impermeable shell containing two lag plugs enclosing the drug plug present in the middle of the unit. So, by erosion, an inert plug leads to drug release. The time taken to erode the inert plug determines the lag time. The shells are made up of plasticizers and biodegradable polymers but the mixture of plugs are pharmaceutical additives

Advantages:

1. It shows better and increased bioavailability and absorption processes than conventional immediate and sustained release dosage forms due to the release pattern being present in a burst manner and targeting the site.
2. Decreases the drug dose without affecting the drug's therapeutic activity.
3. Reduces the side effects compared to other conventional dosage forms.
4. It improves patient compliance nature.
5. Multiple dosing is possible in a single dose of pulse type of system.
6. Less risk of local irritation.
7. Greater stability in dosing.
8. Specific release.
9. To prevent drug loss by first-pass metabolism.

Disadvantages:

1. Large number of manufacturing steps involved in production.
2. Production cost is also high and requires advanced technology.
3. Low drug loading capacity is possible.
4. Lack of manufacturing units.

EVALUATION OF PULSATILE DRUG DELIVERY SYSTEMS :

Evaluation of press coated tablets

Evaluation of rapid release core (RRCT) and press-coated tablets of Atenolol sodium.

Weight variation:

Twenty tablets were randomly selected from each batch weighed individually. The average weight and standard deviation was calculated.

Thickness:

Three tablets from each batch of formulation were collected and the thicknesses of the tablets were measured with the help of Verniercaliper. The average thickness was calculated.

Friability :

Friability of the tablet determined using Roche friabilator. Pre-weighted sample of tablets were placed in the friabilator and were subjected to the 100 revolutions. Tablets were dusted using a soft muslin cloth and reweighed.

Wetting time:

Wetting time of dosage form is related to the contact angle. A piece of tissue paper folded twice was placed in a small petridish containing 6 ml of water. Tablet was kept on the paper and the time for complete wetting was measured.

Disintegration time for RRCTs :

LABINDIA DT 1000 USP disintegration test apparatus. To test the disintegration time of tablets, one tablet was placed in each tube and the basket rack was positioned in a 1 liter beaker containing phosphate buffer pH 6.8 at 37°C ± 1°C such that the tablet remains 2.5 cm below the surface of the liquid. The time taken for the complete disintegration of the tablets was noted.

In-vitro Dissolution methods for press-coated tablets :

In –vitro Dissolution studies of Pulsatile delivery systems was done with the conventional paddle method at 37 ± 0.5 °C using 0.5% w/v aqueous solution sodium lauryl sulfate in USP-II dissolution apparatus at 50 rpm. 5 ml of filtered aliquot was manually withdrawn at pre-determined time intervals and replaced with 5 ml of fresh 0.5% sodium lauryl sulfate solution maintained at the same temperature. The samples were analysed at 342nm using a UV spectrophotometer. The lag time and percentage release was determined of the each formulation.

Release Kinetics:

As a model-dependent approach, the dissolution data was fitted to four popular release models such as zeroorder, first-order, Higuchi and Peppa's- Korsemeyer equations. The order of drug release from matrix systems was described by using zero order kinetics or first orders kinetics. The mechanism of drug release from the matrix systems was studied by using Higuchi equation and Peppa's- Korsemeyer equation. The results are given in Table Q = kot (zero order release kinetics) In (1-Q) = - K1t (First order release kinetics) Q=K2t ½ (Higuchi equation) Mt /Mα = K.tn Peppa's and Korsemeyer equation (Power Law) Where Q is the amount of drug released at time t, K0= zero order rate constant, K1= first order rate constant, K2= Higuchi rate constant, Mt is the amount of drug released at time t and Mα is the

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amount released at time α, thus the Mt /Mα is the fraction of drug released at time t, k is the kinetic constant and n is the diffusion exponent.

Stability Studies:

Stability studies of the optimized formulation of press coated tablets of Atenolol were carried out to determine the effect of formulation additives on the stability of the drug and also to determine the physical stability of the formulation according to ICH guide lines. The studies were carried out at 25oC/60%RH, 30 ºC/65% RH and 40 ºC/75% RH for 90 days by storing the samples in stability chamber (Lab-care, Mumbai).

Post compressional parameters of core tablets Weight variation, Thickness, Hardness, Friability, Disintegration time and wetting time:

The values of weight variation, thickness, hardness, friability and assay of the twenty tablets were found to be within the limits of conventional oral tablets stated in the Indian Pharmacopoeia (IP, 1996). The average mass ranged from 1.18 to 1.62 %, thickness of the tablets varied from 2 mm to 2.5 mm, hardness of the tablets was in the range 4 to 4.5 kg/cm2, the friability ranged from 0.52 to 0.7%. Disintegration time 1.5min to 4min and wetting time 46 to 59 sec. The mass, thickness, hardness, friability, and disintegration time of all compressed tablets were within the limits as per USP.

Release kinetics:

Release kinetics of Atenolol from the optimized formulation P3F3 was found to follow First order kinetics (correlation coefficient, r2 value 0.981).Higuchi plot showed an r2 valve of 0.986 for formulation F3 suggesting that the diffusion plays an important role in the controlled release.

CURRENT SITUATION AND FUTURE SCOPE

Now a day's pulsatile drug delivery is gaining popularity. 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 available in the market. This therapy is mainly applicable where sustained action is not required and drugs are toxic. Key point of development of this formulation is to find out circadian rhythm i.e. suitable indicator which will trigger the release of drug from the device. Another point is absence of suitable rhythmic biomaterial which should be biodegradable, biocompatible and reversibly responsive to specific biomarkers in rhythmic manner. Regulatory is another big question. In preapproval phase it is sometimes difficult to show chronotherapeutic advantage in clinical settings. In postapproval phase causal recreational drug abuse along with on a much larger scale, by the criminal diversion of these modified formulations for profit have arisen problems. The FDA has now heavily relied on the development and implementation of risk management programs as a strategy to allow an approval of a drug to go forward while exercising some restrictions. Many researches are going on the pulsatile drug delivery to discover circadian rhythm with suitable device in the world. In future this delivery will be a leading way to deliver therapeutic agents due to its some unique characters like low chance of dose dumping, patient compliance and the above factors.

II. CONCLUSION:

The circadian rhythm of the body is an important concept for understanding the optimum need for the drug in the body. There is a constant 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 chronic problems such as arthritis, ulcer, asthma, and hypertension. Thus, designing proper pulsatile drug delivery will enhance the patient compliance, optimum drug delivery to the target site, and minimizes the undesired effects

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