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A Review on Pulsatile Drug Delivery System

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Abstract: *In essence, pulsatile drug delivery systems (PDDS) are time-controlled drug delivery systems in which the system regulates the lag time independently of external parameters such as pH, enzymes, gastro-intestinal motility, etc. Traditionally, medications either release immediately or over time. Nevertheless, interest in pulsatile drug release devices has grown recently. These systems were created to work with the body's natural circadian cycle. In Latin literature, Circa and Dian are the words for day and night, respectively. For many medications or treatments, pulsatile drug release—in which the drug is released quickly after a clearly defined lag—could be useful. Asthma, peptic ulcer, cardiovascular disease, arthritis, attention deficit disorder in children, and hypercholesterolemia are among the illnesses where PDDS appears promising. This medication distribution system has been pre-programmed.*

Keywords: PDDS-Pulsatile drug delivery systems; CR-controlled release; SR-sustained release.

I. INTRODUCTION

Pulsatile drug delivery systems (PDDS) are characterized by a rapid drug release after a predetermined lag time and can be classified as single unit (e.g. tablet or capsule) or multiparticulate (e.g. pellets) systems. With the advancement of the technologies in the pharmaceutical field, drug delivery systems have drawn an increasing interest over the last few decades. Nowadays, the emphasis of pharmaceutical galenic research is turned towards the development of more efficacious drug delivery systems with already existing molecule rather going for new drug discovery because of the inherent hurdles posed in process. A second-generation drug delivery goal has been the perfection of continuous, constant rate delivery of bioactive agents. However, living organisms are not ‘‘zero-order’’ in their requirement or response to drugs. They are predictable resonating dynamic circadian cycle which will maximize desired and minimize undesired drug effects. Till early nineties efforts have been made to design the drug delivery system which will release the drug at fairly constant rate.

Table 1: Diseases requiring Pulsatile Drug Delivery:

DISEASE	CHRONOLOGICAL BEHAVIOR	DRUGS USED
Peptic ulcer	Acid secretion is high in the afternoon and at night	H2 blockers
Asthma	Precipitation of attacks during night or at early.	Antihistaminic , β2agonist,
Cardiovascular Diseases	BP is at its lowest during the sleep cycle and rises steeply during early morning awakening period	Nitroglycerin Calcium channel blockers
Arthritis	Pain in the morning and more pain at night	NSAIDs Glucocorticosteroids
Diabetes mellitus Attention	Increase in the blood sugar level after meal	Sulfonylurea, Insulin, Biguanide
Hyper cholesterolemia	Cholesterol synthesis is generally higher during night than day time	Hmg CoA reductase inhibitors

II. POLYMERS USED IN PULSATILE DRUG DELIVERY SYSTEM:

Pulsatile drug delivery systems are necessary for applications where continuous release of the drug would be harmful and repeated dosing would be difficult, painful, or otherwise problematic. A prime example is the administration of

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insulin to treat diabetes. To ensure effective treatment, the level of insulin release must be very low in general, but significantly higher after a meal. Other examples of the desirability of administering pulsating medications include the administration of blood pressure medications and immune boosters, and many hormone therapies. The pumps have been successfully used to deliver pulsatile medications and are now being used in several diabetic patients. However, they have limitations, notably the need to pull tubes through the skin, creating pathways for infection. Fully implantable systems would reduce this risk. The system proposed by Langer and coworkers exploits the wide adaptability of biocompatible polyesters in the poly(lactic-co-glycolic acid) (PLGA) family of biodegradation. By changing the relative amounts of lactic acid and glycolic acid in the copolymer, as well as the molecular weight of the copolymer, the degradation rate of the material can be controlled and varied widely.

To release bursts of drug at different times, several PLGA copolymers with different degradation rates were used as 'gatekeepers'. Each copolymer was designed to hold back a burst of drug until that particular membrane had degraded sufficiently toallow the drug to escape. With this system, Langer and colleagues were able to achieve pulsatile release of several types of 'model drugs' with different properties. The drug-delivery system is based on a microchip formed from poly (Lactic acid), the mostslowly degrading of this polyester family.

Furthermore, because the drug molecules are stored in a reservoir rather than suspended in the polymerformulation, this system should be compatible with a wide variety of drugs. For example, heparin – a common anti- coagulant that is hydrophilic bioactive after incorporation into and release from this drugdelivery system, even after 140 days. The superb performance of this new device, along with the longtrack record for safety and biocompatibility of thepolymer materials used to fabricate the device, bode well for success in a variety of clinical applications. The next advance in pulsatile drug delivery is likely to be systems in which release from an implant can be actively modulated, to increase or decrease dosingin response to demand.

Ideally, such systems will later be coupled with biosensor devices so that drug delivery can respond to physiological cues in real time. Insulin release from the implant can be correlated with a glucose sensor, allowing tighter blood sugar control and reducing the effects of diabetes. Drug release from polymeric systems can be controlled by externally generated ultrasound energy that can be safely used outside the body and generated by a small portable sensor. In another example, thermosensitive polymer composites with near-infrared light-absorbing nanoparticles have been shown to undergo significant phase changes in response to infrared light. This may be useful as a drug delivery system that releases medication from a light source the size of a laser pointer on external light. These stimuli-responsive systems presumably offer greater control and flexibility than systems based on intrinsic differences in polymer degradation, but are also more complex and expensive. The potential advantages of pulsed dosing regimens in various conditions will ensure high interest in modular drug delivery systems in the future, and advances in materials science will greatly improve our capabilities in this area of drug delivery.

2.1 Classification of Pulsatile Systems

Single-unit systems and multiple-unit systems are two different types of pulsatile systems. Single-unit systems can be designed as osmosis- or capsule-based systems. In the design of single-unit systems, the system is coated with either an eroding/soluble or rupturable coating. Yet in multiple-unit systems, the pulsatile release is brought about by altering the permeability of the membrane or by coating the system with a rupturable membrane.

Single Unit Pulsatile Systems

These are sub-classified as capsule-based systems, osmotic systems, delivery systems with soluble or erodible membranes, and delivery systems with rupturable coating.

Capsule Based Systems

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 as a "Pulse" from the insoluble capsule body. Pulsincap® 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. A swellable hydrogel plug was used to seal the drug contents into the capsule body [4]. When this capsule came in contact with the dissolution fluid, it swelled; and after a lag time, the plug

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pushed itself outside the capsule and rapidly released the drug. Polymers used for designing of the hydro gel plug were various viscosity grades of hydroxyl propyl methyl cellulose, poly methyl methacrylates, poly vinyl acetate and poly ethylene oxide. The length of the plug and its point of insertion into the capsule controlled the lag time.

Systems based on osmosis

The Port® system was developed by Therapeutic system research laboratory Ann Arbor, Michigan, USA, and consists of a capsule coated with a semipermeable 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

Drug delivery system with rupturable layers/ membranes

These systems are based upon a reservoir system coated with a rupturable membrane. The outer membrane ruptures due to the pressure developed by effervescent agents or swelling agents. Sungthongjeen *et al*. designed a pulsatile drug delivery system where the tablets of buflomedilHCl prepared by direct compression with varying amounts of spray-dried lactose and microcrystalline cellulose were coated with an inner swelling layer using croscarmellose sodium and an outer rupturable layer using ethyl cellulose. It was observed that by increasing the amount of ethyl cellulose coating, the lag time could be prolonged. Ethyl cellulose, being water insoluble, retarded the water uptake. Similar results were obtained with croscarmellose sodium. Increasing the amount of microcrystalline cellulose decreased the lag time substantially

Multiple unit pulsatile systems

More reliable gastric emptying patterns are observed for multiparticulate formulations as compared to single-unit formulations, which suffer from 'all or none' concept. As the units of multiparticulate systems are distributed freely throughout the gastrointestinal tract, their transport is affected to a lesser extent than single-unit formulations by the transit time of food

III. ADVANTAGES OF PULSATILE DELIVERY

1. Pulsatile drug delivery system has a less side effects.
2. It is feasible to maintain dosage frequency.
3. This technology reduces dose size.
4. Patient compliance increases due to low dose and minimum dosage frequency.
5. It also provide target specific action to colon.
6. Drug loss is avoided due to extensive First pass metabolism.

IV. DRAWBACKS OF PULSATILE DELIVERY

1. Manufacturing reproducibility and efficacy is less.
2. There are large number of process variables.
3. It requires multiple steps for formulation.
4. It needs advanced technology.

V. RECENT ADVANCEMENT IN PDDS

In comparison to immediate-release formulations, pulsatile-release formulations have various benefits. These formulations make it easier to administer medications less often, which can boost patient compliance. The possibility of systems that can release pharmaceuticals after a programmable lag period starting at administration time, or in a pulsatile mode, has recently attracted more attention in the field of drug delivery. Technologies for ensuring the time-controlled pulsatile release of bioactive substances have been developed over the past 20 years. The development of pulsatile drug delivery systems that can successfully treat diseases like diabetes that require non-constant dosage

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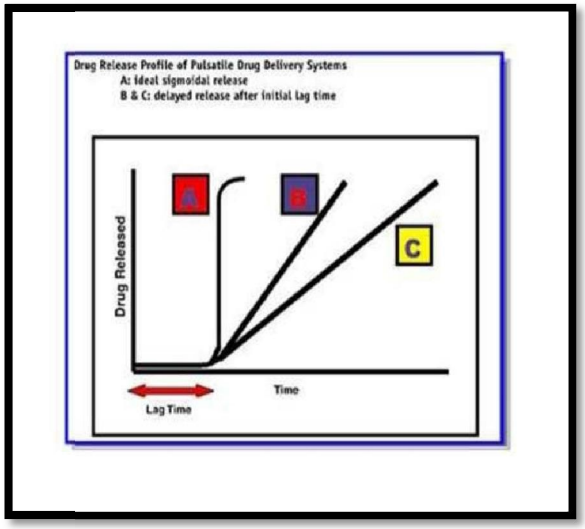
therapies has advanced significantly. To carefully illustrate the pulsatile transport of bioactive chemicals, particularly hormones, there is still much study to be done.

Ultrasound Pulsatile Drugs Delivery Systems

Ultrasound has been one of the methods used in recent decades for diagnostic imaging in the medical field. The idea of joining ultrasound with drugs has initiated interest in different clinical fields entered the field of cancer therapy, where it was called "sonodynamic therapy," as well as, for the treatment of diabetes. As for drug delivery, sound waves will be used to stimulate drug release from carriers and enhance vascular permeability. Drug release in a pulsed manner could be achieved by corrosion of the polymeric matrix.

When ultrasound is spread in body tissues, the drug release will be stimulated through several resulting effects which are usually pressure acoustic fluid streaming, cavitation, and local hyperthermia.



ACCU-BREAK Technology

In this technology, formulation splits itself to small tablets of exact dosage form, thus dose adjustment becomes simple. In ACCU-T-CR tri-layer tablets, tablets contain control release medication and immediate release ingredients.

TMDS Technology

The time multiple action system provided control release rate of multiple ingredients within a single dose

GEOLOCK Technology

This technology contains press-coated tablet in which the active drug stays surrounded by an additional hydrophobic wax layer.

DUREDAS Technology (Dual Release Drug Absorption System) Here bilayer tablets were manufactured. One layer released immediately and other layer release after some time which is predetermined.

KV/24

In this, one or more drugs are remaining encapsulated to release drug in predetermine manner. Neutral core which is coated previously is again coated with drug to achieve drug release profile once a day .

INNOHERB

It contains pallets coated with polymer and kept in capsule shell. It contains herbal compound.

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IPDAS Technology (Intestinal Protective Drug Absorption System)

It involve high density compressed form of drug with control release. Normally drug release immediately in GIT but to create control release of drug, bead matrix or semi permeable membrane are used. It comes under multiparticulate system.

ORBEXA Technology

It comes under multiparticulate in which high drug loaded and product is subject to granulation. After performing further process beads are created and coated with functional polymer.

VI. FUTURE SCOPE

As in some disease conditions, the prospect of chronotherapy and pulsatile delivery of drugs seems to be very optimistic in future. Pulsatile drug delivery strategies acquire time-controlled and site- specific dosage of single or multiple devices. Pulsatile flow in formulation is achieved by use of different kind of polymers and thickness of coating layer also control the rate release of active pharmaceutical ingredient.

VII. CONCLUSION

The development of a continuous, regulated drug delivery system, which is usually successful in reducing drug consumption, receives excessive attention due to its positive effects. This type of formulation releases the active ingredient to the specific site of action at the appropriate moment, but it does not do so in a circadian-like fashion. Technology advances and the availability of all necessary supplies have caused the pharmaceutical industry to expand quickly as well. These developments have led to the creation of formulations that release in a specific way by adhering to the body's circadian rhythm. Comparing controlled/sustained release drug delivery systems with traditional dosage forms will show that the former are much superior, and that the latter have greater advantages over sustained release formulations.

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