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A Review on Chronopharmaceutical Drug Delivery System

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A B S T R A C T

Pulsatile Drug Delivery systems (PDDS) are basically time-controlled drug delivery systems in which the system controls the lag time independent of environmental factors like pH, enzymes, gastro-intestinal motility etc. These systems are designed according to the circadian rhythm of the body. The pulse has to be designed in such a way that a complete and rapid dug release should be achieved after the lag time. In recent years, pulsatile drug release systems are gaining importance in the clinical therapies includes asthma, peptic ulcer, cardiovascular diseases, arthritis, attention deficit syndrome in children, and hypercholesterolemia where night time dosing is required. Therefore Pulsatile drug delivery is one such systems that became trendy by delivering drug at the right time, right place and in right amounts, holds good promises of benefit to the patients suffering from chronic diseases.

Keywords: Cinnarizine, HPMC, Drug release kinetics, Ethyl cellulose, Diffusion exponent (n)

A R T I C L E I N F O

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1. Introduction

In the advancement of the technologies in the pharmaceutical field, drug delivery systems have drained 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 drug discovery and development process. Traditionally,

drug delivery has meant for getting a simple chemical absorbed predictably from the gut or from the site of injection. The oral controlled release system shows a typical pattern of drug release in which the drug concentration is maintained in the therapeutic window for a prolonged period of time (sustained release), thereby ensuring sustained therapeutic action. A second-generation drug delivery goal has been the perfection of continuous, constant rate delivery of bioactive agents.

Further, in case of chronic treatment, where the drug is given in sustained release dosage form, continuous exposure of the drug to body may lead to adverse effect. For example, diabetes mellitus requires chronic treatment with sustained release formulations of drugs like sulfonylurea which will damage the pancreas earlier than the corresponding immediate release dosage form. Lastly, drugs which exhibit tolerance should not be delivered at a constant rate, since the drug effect decreases with time at constant drug level. In addition drug toxicity increases with time when drug levels are held constant. In such cases it is preferable dosage form which will provide desired concentration of drug at particular time point only. Nowadays, concept of chronopharmaceutics has emerged, wherein, research is devoted to the design and evaluation of drug delivery systems that release a therapeutic agent at a rhythm that ideally matches the biological requirement of a given disease therapy(1,2).

Diseases where a constant drug levels are not preferred, but needs a pulse of therapeutic concentration in a periodic manner acts as a push for the development of "Pulsatile Drug Delivery Systems". In these systems, there is rapid and transient release of a certain amount of drug molecules within a short time-period immediately after a predetermined off release. Various techniques are available for the pulsatile delivery like pH dependent systems, time dependent systems, micro-flora activated systems, etc. which can be designed as per the physiology of disease and properties of the drug molecule. The focus of the present review is primarily on the pulsatile drug delivery methodologies and the upcoming technologies, which are being exploited on an industrial scale(3).

2. Chronotherapeutics

It is the purposeful delivery of medications in unequal amounts over time during 24 hours. Chronotherapeutics takes into account rhythm determinants in disease pathophysiology, chronopharmacology of medications, dose and administration time to optimise desired/ minimise adverse effects. Chronotherapeutics does not involve only new medicines but also the improved applications of established once in a different and more biologically efficient manner.

In certain instances, chronotherapeutics may be achieved by unequal morning and evening dosing schedules of sustained release 12 hours medication systems, better timing of conventional once a day medication/delivery systems, or application of special tablet and capsule formulations dosed at designated times to proportion medications over 24 hours in synchrony with rhythm determined requirements. The current generation drug delivery systems used in chronotherapeutics demands strict adherence by patients to recommended dosing time to achieve desired outcome. "The goal of chronotherapeutics is the management or reversal of existing acute or chronic medical conditions" & "Delivery of drugs to the body to the right site, at the right time, at optimal dose"(4,5).

Table 1: Drugs that have been developed or are under development for Chronotherapy

Class	Drugs
Cardiovascular drugs	Verapamil, Propranolol, Diltiazem, Nifedipine, Enalapril
Antiasthmatic drugs	Methylprednisolone, Prednisolone, Albuterol, terbutaline, Theophylline
Anticancer drugs	Cisplatin, Oxaliplatine, Doxorubicin, 5- fluorouracil,
Non steroidal anti-inflammatory drugs	Ibuprofen, Ketoprofen, Indomethacin, Tenoxicam
Anti ulcer drugs	Cimetidine, Ranitidine, Famotidine, Pirenzipine, Omeprazole
Anticholesterolemic drugs	Simvastatin, Lovastatin

Oral controlled drug delivery systems release the drug with constant or variable release rates. These system shows a typical pattern of drug release in which the drug concentration is maintained in the therapeutic window for a prolonged period of time (sustained release), thereby ensuring sustained therapeutic action. But there are certain conditions which demand release of drug after a period of no drug release which is known as lag time. Diseases where constant drug levels are not preferred, but needs a pulse of therapeutic concentration in a periodic manner acts as a push for the development of "Pulsatile Drug Delivery Systems"(6).

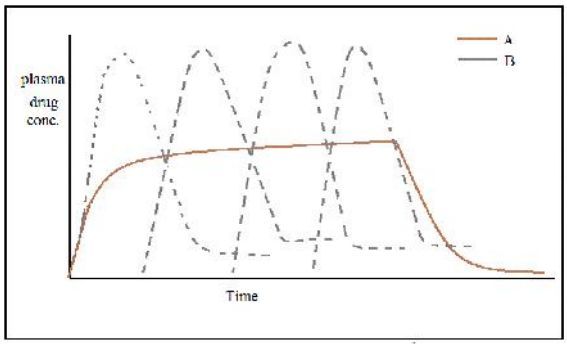

Figure 1: Release pattern of Sustained Release Dosage Form (A) and Pulsatile Release Dosage Form (B).

A delivery system with a release profile that is characterized by a time period of no drug release (lag time) followed by a rapid and complete drug release (pulse release) can be called as an ideal pulsatile drug delivery system. In other words, it is required that a drug should not be released at all during the initial phase of dosage form administration. Lag time is defined as the time between when a dosage form is placed into an aqueous environment and the time at which the active ingredient begins to get released from the dosage form; precisely lag time is an interval of no drug release followed by rapid drug release [7].

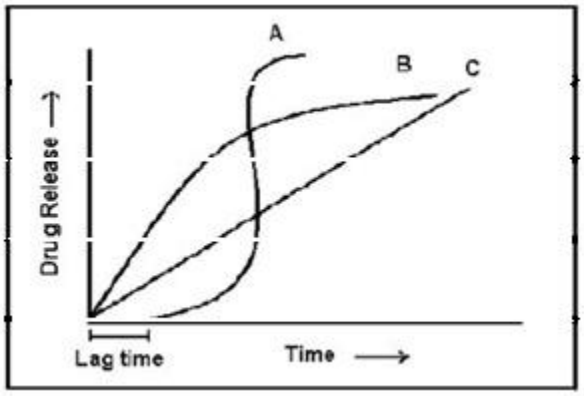

Figure 2: Drug release profiles (A) Pulsatile, (B) Conventional and (C) Extended release.

Pulsatile Drug Delivery System

Pulsatile drug delivery system is time and site-specific drug delivery system, thus providing special and temporal delivery and increasing patient compliance. Pulsatile drug delivery system is defined as the rapid and transient release of certain amount of molecules within a short time period immediately after a predetermined/programmable off-release period, i.e., lag time (Kikuchi and Okano, 2002). They are predictable resonating dynamic systems, which require different amounts of drug at predictably different times within the circadian cycle(8).

Mechanism of Drug Release from Pulsatile Drug Delivery System

The mechanism of drug release from PDDS can be occurring in the following ways

Diffusion:

Water diffuses into the interior of the particle when particle come in contact with aqueous fluid in the gastrointestinal tract and resultant drug solutions diffuse across the release coat to the exterior [9].

Erosion: Some coatings designed to erode gradually with time, result in the release of drug contained within the particle.

Osmosis: An osmotic pressure can be built up within the interior of the particle when water allows entering under the right circumstances. The drug is forced out of the particle into the exterior through the coating (10).

3. Classification of Pulsatile Drug Delivery Systems

Pulsatile systems can be classified into single- and multiple-unit systems. Based on methodologies, pulsatile drug delivery system can be broadly classified into three classes;

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

a) Time Controlled Single Unit Pulsatile Systems

The principle of time controlled drug delivery systems is that the release of the drug happens according to a predetermined rate after a lag phase (delayed release systems) to achieve maximum therapeutic and minimum toxic effect. These are sub-classified as capsule-based systems, osmotic systems. Single-unit systems are designed by coating the system either with eroding/soluble or rupturable coating [11].

Time controlled single unit capsule based systems with release controlling plug

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 i.e., Pulsincap.

Pulsincap:

It is a single unit system comprised of a water insoluble capsule body enclosing the drug reservoir. The capsule body is closed at one end with a swellable hydrogel plug. When the capsule comes in contact with water it absorbs water and swells. After a lag time the plug gets pushed out and the drug gets release rapidly in the form of a pulse. Rapid release of the drug can be ensured by the inclusion of effervescent agents, super disintegrants and osmotic agent(12,13).

Pulsincap was developed by R. P. Scherer International Corporation, Michigan, US. The system comprises of a water-insoluble capsule enclosing the drug reservoir and a highly swellable, erodible or lipophilic matrix plug made of approved substances such as hydrophilic polymers or lipids was used to seal the drug contents into the capsule body. This plug undergoes a timed removal either because of its water swelling and/or erosion processes or following a pressure rise that is caused by water uptake inside the capsule body. 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 rapidly releases the drug. Various types of polymers used for designing of the hydrogel plug are Ethyl cellulose, hydroxyl propyl methyl cellulose (HPMC), polyvinyl alcohol (PVA), poly methyl methacrylates, polyvinyl acetate and polyethylene oxide. The length of the plug and its point of insertion into the capsule controlled the lag time. When capsule made an enteric coating, the system was evaluated for time-dependent colon delivery as well. In this respect, scintigraphic investigations indicated that a selective plug ejection in the large bowel could be achieved [14, 15].

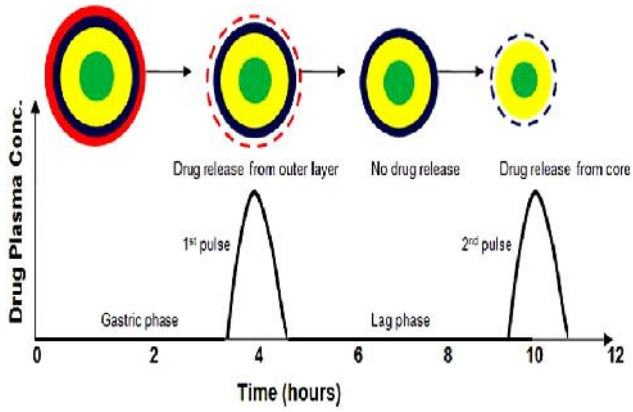

Figure 3: Drug release pattern after lag-time

b) Drug Release Pattern

Pulsatile drug delivery system is defined as the rapid and transient release of certain amount of drug molecules within a short time period immediately after a predetermined off-release period, i.e., lag time. Pulsatile drug delivery aims to release drug on programmed pattern i.e. at appropriate time and at appropriate site of action. A single dosage form provides an initial dose of drug followed by one release free interval, after which second dose of drug is released, which is followed by additional release-free interval and pulse of drug release. The pulsatile effect, i.e., the release of drug as a "pulse" after a lag time has to be designed in such a way that a complete and rapid drug release should follow the lag time may not always be desirable.

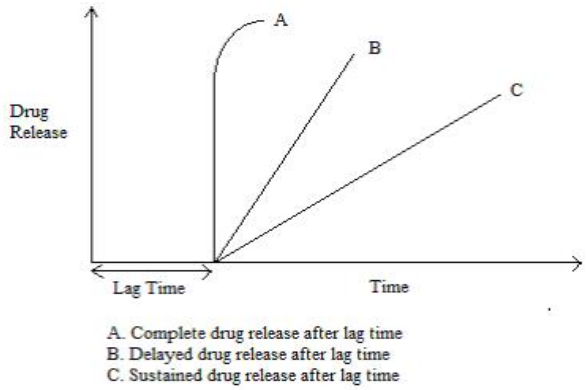

Figure 4: Drug release Profile of Pulsatile Drug Delivery System

5. Various Technologies of Pulsincap Drug Delivery

Many technologies have been developed to deliver the drugs to the body according to the biological rhythm of the disease. The technologies developed to achieve this aim are described below [16].

Diffucaps Technology

Developed by Eurand Pharmaceuticals Ltd,USA**.** Diffucaps is a multiparticulate bead system comprised of multiple layers of drug, excipients and functional polymer membrane to control the rate of drug release. Diffucaps beads are <1.5 mm in diameter and can be filled into capsules. The beads contain a layer of organic acid or alkaline buffer to control the solubility of a drug by creating an optimal pH microenvironment for drugs that exhibit poor solubility in intestinal pH, environmental pH greater than 8.0 or in physiological fluids. Alternatively, the beads can contain a solid solution of drug and crystallization inhibitor to enhance bioavailability by maintaining the drug in its amorphous state(17). Advantages of Diffucaps are

- Ideal for drugs exhibiting poor solubility in lower intestinal pH, in environments with pH above 8.0, or in physiological fluids.
- Can combine multiple drugs and/or multiple release profiles in the same dosage form.
- Can minimize food effect.

Contin Technology

Developed by Purdue Pharma. This technology provides for closer control over the amount of drug released to the bloodstream, and benefits patients in terms of reducing the number of doses they need to take every day, providing more effective control of their disease (particularly at night), and reducing unwanted side effects. Molecular coordination complexes are formed between a cellulose polymer and a non-polar solid aliphatic alcohol optionally substituted with an aliphatic group by solvating the polymer with a volatile polar solvent and react the solvated cellulose polymer directly with the aliphatic alcohol, preferably as a

melt. This constitutes the complex having utility as a matrix in controlled release formulations since it has a uniform porosity (semi permeable matrixes) that may be varied**.** This technology has leads to the development of tablet forms for aminophylline, theophylline, morphine, and other drugs(18).

CODAS (Chronotherapeutical oral drug absorption system) technology

Élan Corporation, USA, developed CODAS technology. Delay is introduced by the level of non-enteric release-controlling polymer applied to drug loaded beads. The release-controlling polymer is a combination of water soluble and water insoluble polymers. As water from the gastrointestinal tract comes into contact with the polymer-coated beads, the water soluble polymer slowly dissolves, and the drug diffuses through the resulting pores in the coating. The water insoluble polymer continues to act as a barrier, maintaining the controlled release of the drug(19,20).

PORT technology

The Programmable Oral Release Technologies (PORT) system is a uniquely coated, encapsulated system that can provide multiple programmed release of drug . It contains a polymeric core coated with a semi-permeable, rate-controlling polymer. Poorly soluble drugs can be coated with solubilizing agents to ensure uniform controlled release from the dosage form. In capsule form had gelatin capsule is coated with a semi-permeable, rate-controlling polymer. Active medicament mixed with osmotic agent is kept inside capsule shell. A water-insoluble plug is used to seal the capsule shell. Immediate release compartment can be added according to need [21].

Table 2: Marketed Formulations of Pulsincap Technology

Technology	Mechanism	Proprietary Name and dosage form	Api	Disease
OROS*	Osmotic Mechanism	Covera-H5*; XL Tablet	Verapamil HCL	Hypertension
Three dimentional printing*	Externally regulated system	Their Form*	Diclofenac Sodium	Inflammation
DIFFUCAPS*	Multiparticulate System	Innopran*; XL Tablets	Verapamil HCL, propranoll HCL	Hypertension
PulsincapTM	Rupturable system	PulsincapTM	Dofetilide	Hypertension

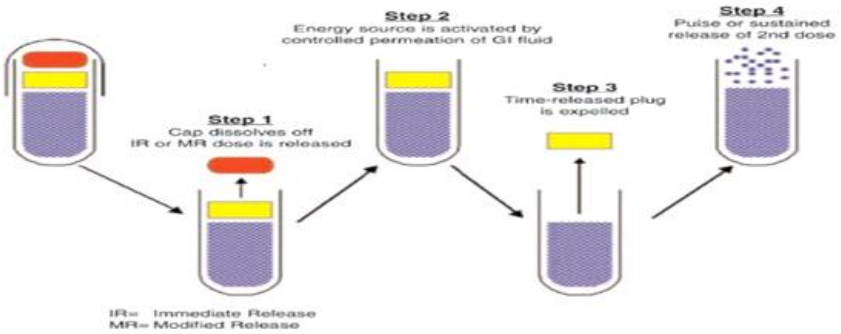

Figure 5: Port System of Pulsatile Drug Delivery System

Advantages:

- The System is cost effective
- Improved the bioavailability
- Flexibility in design
- Improved stability
- Reduced dose size and no risk of dose dumping
- Reduced side effects

Drug targeting ton specific site like colon

4. Conclusion

Different technologies have been applied to develop time-controlled, pulsed, triggered and programmed drug delivery devices in recent years. A major progress has been achieved towards chronopharmaceutical drug delivery systems that can effectively treat disease with non-immediate dosing therapies such as diabetes. Products that are currently under development for commercialization are for the delivery of proteins, hormones, pain medications and other pharmaceutical compounds. This new approach to the development of novel drug delivery system ChrDDS (Chronotherapeutical Drug Delivery System) of drug administration in disease therapy has significant impact upon treatment diseases like peptic ulcer, asthma, cardio vascular diseases. ChrDDS in future is certainly going to gain popularity. Chronopharmaceutics will certainly improve patient outcome and optimize disease management in the future.

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