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A Recent Approach On: Pulsatile Drug Delivery System

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ABSTRACT:

Pharmaceutical invention are increasingly focusing on rapid drug delivery systems which enhanced desirable therapeutic objectives while decreasing side effects. Recent trends indicate that drug delivery systems are especially suitable for achieving controlled or delayed release oral formulations with low risk of dose dumping, flexibility of blending to achieved desirable release patterns with less inter- and intra-subject variability. A pulsatile principles of drug delivery system seems to present the advantage that a drug can be released in the GI tract after a definite time period of no drug release. Pulsatile drug delivery system (PDDS) concept was applied to increase the residence of the dosage form having lag phase followed by a burst release. Diseases wherein PDDS are promising include Hypertension, asthma, peptic ulcer, cardiovascular diseases, arthritis, and attention deficit syndrome in children. PDDS works on principle of time-controlling system like swelling and Repturable membranes, soluble or erodible coating, capsule-shaped system, and multiparticulate system are primarily involved in the control of release. PDDS showed excellent lag phase followed by burst release in distal part of small intestine which gives site- and time-specific release of drugs acting as per chronotherapy of the diseases.

KEYWORDS:Pulsatile drug delivery system, Controlling plug, Eroding or soluble barrier, Multiparticulate, Repturable coating

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Introduction

As advancement in pharmaceutical technology, delivery of drug has drawn an attention over last few years. Recently the pharmaceutical researcher has moved for development of novel and more efficacious way for drug delivery with already existing drug entities. In past few years development of controlled release formulation which provide constant plasma release drug profile but due to constant release of drug in body at regular interval of time cause problem like resistance, side effect and tolerability. Besides of targeted, controlled, sustained prolonged and targeted drug delivery system which proved to successfully delivery of drug molecule, a pulsatile drug delivery system has focused to scientist which is based on the concept of Chrono-therapeutics.[(1)]

Pulsatile Drug Delivery System

In past few years, the value of pulsatile drug delivery system is increased and lot of attention is made now a day. The pulsatile drug delivery system is characterized by pre-programmed drug release (lag time).[(2)] The pulsatile drug delivery system release the drug at specific site at the specific time and in specific amount, thus maintaining spatial and temporal drug delivery

which ultimately increase patients compliance.[3]The design of drug delivery as a pulse release is done in such a way that complete and rapid drug release occur after a pre-programmed lag time.[4]It targets the drug to release in a programmed manner at specific time as per need of disease condition which results in improving patient compliance and its therapeutics efficacy.[5]The pulsatile systems are designed as per circadian rhythm of human body. The main objective for the use of pulsatile drug release is that the drug where constant drug release i.e., zeros order is not important.[6]

Controlled drug release system have attain a very promising place in pharmaceutical research and development in maintain constant plasma drug concentration within the therapeutic window for long period of time in human body. For this reason more attention and interest increased in development and formulation of controlled drug delivery system. These dosage forms have many advantages as compared to conventional dosage form such as constant plasma drug level at the site of action, decrease in dose of drug and administration frequency, prevention of side effect and improved patients compliance.[7]But there are many situation/conditions where controlled release pattern are notdesired. In these conditions the drug release after a pre-programmed lag time is achieved for better therapeutics efficacy. In other words drug should not release at initial phase of drug administration. These release patterns is known as pulsatile drug delivery system.[8]

Oral Pulsatile Drug Delivery System

In the era of modified drug release, pulsatile drug release system is gaining more interest as it liberates the drug molecules following a programmable lag phase from the time of drug administration. Pulsatile drug delivery system intended for oral route is beneficial to disease based on chronotherapy like bronchial asthma, angina pectoris, peptic ulcer, arthritis, diabetes mellitus, hypertension and hypercholesterolemia. Upto early nineteenth century great emphasis have made in designing the drug delivery system which will be able to release active ingredient over extended period of time. Many delivery system such as controlled, prolonged, extended etc. have developed but more attention have shift to innovative Chronotherapeutic based drug delivery system. It has been noticed that 24 hours variation circadian rhythm prevailing over shorter and longer temporal cycles with adaptation to light-darkness alteration which have high impact on number of therapy and diagnoses.[9]

Many disease states follow biological rhythm as short, intermediate and long period oscillation cycles. Circadian (24 hours) is most common oscillation in pathological cases like duodenal ulcer where gastric acid secretion is maximum at midnight, bronchial asthma exhibit more serious dyspnoea episode in night or in early morning, ischemic heart attack and in rheumatoid arthritis where pain is maximum at morning. In hypertension where increase in blood pressure attend peak at early morning and in hypercholesterolemia the cholesterol synthesis is more during the night.[10]

Condition that demand pulsatile drug delivery system.[11, 12]

(a) Drug which undergo first-pass metabolism result in reduced bioavability,disturb steady state level of drug and its metabolites.

(b) For colonic drug delivery system, drug targeted to distal organs of GIT should be protected that release of drug in upper GI tract not occurs.

(c) Many body organs follow circadian rhythm like acid secretion, gastric emptying rate, hormone secretion and gastrointestinal blood transfusion.

(d) Disease showing circadian rhythm in their pathophysiology like hypertension ulcer, myocardial infarction, rheumatic arthritis and bronchial asthma.

(e) Drugs producing biological tolerance demand a system which prevent therecontinuous presence at bio phase as it reduce their therapeutic effect.

(f) Drugs which undergo degradation in gastric acid medium irritate to gastricmucosa and cause nausea and vomiting, lag time is essential in preventing them.

CHRONOPHARMACOLOGY

Dosing time dependencies[13]

The major affection of the time of day on drug efficacy its toxicity is not surprising because most of mammalian physiologies are affected by the circadian clock. Recently most approaches consider the prelevance of dosing time for drug effect to recommend a standard best time for drug administration in populations with well-

synchronized circadian physiology. Recently acquired knowledge on the circadian timing system and the availability of new experimental and computational models and technologies now allow for the identification of the key clock and clock- controlled components that influence the dynamics of drug effects.

Chronobiology[14]

Chronobiology is the analysing of biological rhythms and the mechanisms of biological timekeeping. From early times rhythmicity has observed in plants and animals. In Fourth century BC, Alexander has noted that certain leaves of tress opened during the day and closed during the night which shows completely rhythmicity.

Biological rhythm

The biological rhythm is self-sustaining oscillation of endogenous origin. Every endogenous biological process and there function are programmed in time during 24 hours for the conduction of specific activities at different times. Biological rhythm is characteristics of period, level, amplitude and phase.

Period: Period is the time duration which required completing a single cycle.

Level: The baseline around which rhythmic variation occurs is known as level.

Amplitude: The measure of magnitude of predictable in time variability dueto Biological rhythm is known as amplitude

Phase: Phase means a clocking of specific features like peak and trough values, of a Rhythm relative to corresponding time scale.[15]

There are three types of mechanical rhythm in our body:

1. **Ultradian rhythm**
2. **Infradian rhythm**
3. **Circadian rhythm**

Ultradian rhythms:

This rhythm which have a period shorter than 24 hours. E.g. time taken by a nerve impulse to be transmitted.

Infradian rhythms:

These rhythms having a frequency which change from 28 hours to 6 days.

Circadian rhythms:

Circadian cycles last about 24 hours. The word "Circadian", coined by Franz HalBerg, comes from Latin words circa means "around", and dian means "day", means "approximately once a day".

Circadian cycles are important in determining the sleeping and feeding pattern of animals and human beings. The patterns which follow the circadian cycle are core body temperature, brain motor activity, secretion of hormones, and other biological activities. Every people function in different ways. Some people are best in morning while other have peak maxima at noon or evening. Many people face difficulty in adjusting to shift work schedules.[16]

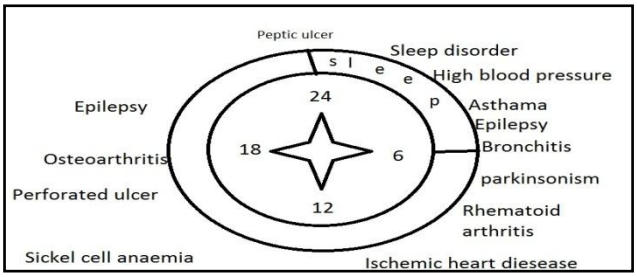

Figure 1: Human circadian time structure.[14]

Circadian clock

The behaviour, physiology, and biochemistry of organisms changes rhythmically over 24 hours. The rhythms are generated by "clock gene" encoded with genetic instruction which produce proteins whose level oscillates in the course of one day. The synchronizer routine of human beings sleep in darkness from 10:30 p.m. to 6:30 a.m. and activity started from 6:30 a.m. to 10:30 p.m. Disturbance in these circadian clock make imbalance in daily body function. Certain condition like day/night variation in asthmatic dyspnoea, secretion of acid in midnight, blood pressure attains peak maxima at early morning etc. result due to disturbance in circadian clock.[15]

Circadian time structure and there implication

Circadian rhythm is controlled by master clock network which is composed of suprachiasmatic nuclei located in

hypothalamus and pineal gland. The clock gene like per1, per2, per3, CRY and nocturnal secretion of melatonin from pineal gland control the time keeping mechanism. The master clock network which orchestrates the period and phase of circadian clock situated in cell, tissues and other organs system. The major environmental changes involved in circadian is daily changes in light intensity. Mostly human beings sleep in darkness from 10:30 p.m. to 6:30 p.m. and perform the activity in light of day during 6:30 a.m. to 10:30 p.m. The maximum valley peak of gastric acid secretion, white blood cell count and calcitonin gene protein occur at midnight or at early in sleep. The blood lymphocytes, thyroid stimulating hormone, prolactin level and eosinophil count reach maximum during sleep. The rennin activity, angiotensin and aldosterone level reach peak maxima in early morning. The peak of insulin and haemoglobin occur at noon and in afternoon. The cholesterol level, triglycerides and urinary diuresis occur early in morning as shown in figure 2. The physiology and biochemistry of human being is not over constant for 24 hours but it changes in predictable manner by timing of peak trough of body circadian rhythm.[17]

Necessity of Pulsatile Drug Delivery System

Although sustained release formulation maintain constant plasma drug concentration but there are certain disease and condition where sustain release of drug is not desired because it cause side effect and not shows good efficacy and poor patience compliance. In such condition the release of drug after a lag time means drugs is not release at its initial phase of drug administration. In such situation pulsatile drug delivery system is applicable.[18]

(a) Drug which undergoes degradation in acidic pH, lag time is important fordelivery of such drug. E.g. peptide drug[18]

(b) Condition in which severity of disease occurs like bronchial asthma, ulcer,angina pectoris, hypertension and rheumatic diseases time dependent.[19]

(c) For targeting and localized action at distal organ of GIT such as colon, drug should prevent in the upper GI tract. E.g. ulcerative colitis[18]

(d) Drugs which undergo extensive first pass metabolism results in decreased in bioavability. E.g. beta-blocker[19]

(e) Drugs which produce biological tolerance demand a system that prevents its continuous release at site of action as this tends to reduce their therapeuticeffect. E.g. salbutamol sulphate.[19]

(f) Many body organs and there function follows circadian rhythm. E.g. hormonesecretion like rennin and aldosterone, acid secretion, gastric emptying time and blood transfusion.[18]

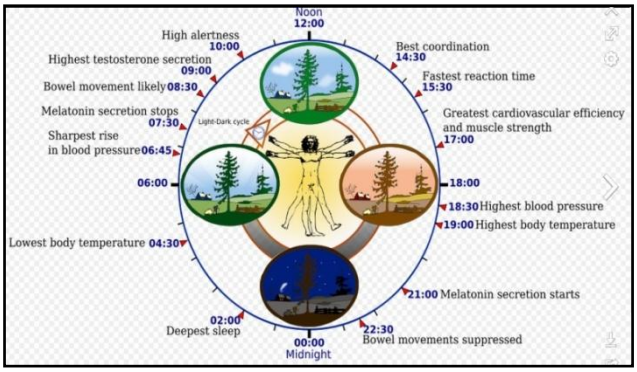

Figure 2: Human circadian rhythm (24 hrs) biological clock

Chronotherapeutic

Chronotherapeutic deals with the delivery of treatments which is based on the dynamic changes observed with drug pharmacology effect and disease-related processes. The primary requirement of approaches of Chronotherapeutic is the determination of an optimal dosing time of drug to reduce the toxicities and efficacy is improved. Chronotherapeutic not only involve in new medicines but also to improved applications of established once in a different and more biologically efficient manner. In certain situation, Chronotherapeutic may be achieved for unequal morning and evening dosing schedules for sustained release 12 hours medication systems. Chronotherapeutic does not deals to drug release in constant profile as seen in sustained drug release system but it release the drugs after the pre-programmed lag time achieved by the system.[20]

Potential role of Chrono therapy in common disease

Many common clinical diseases depend on circadian variation in onset of Exacerbation of system. Specific therapy and dosage are employed (sustained release) to targeted the specific site but the disease which shows changes as per circadian cycle are not desirable, in such situation chronotherapy pulsatile release of drug is achieved to control the effect which has alleviated at specific time interval.[21]

Asthma: Asthma are the most common disease in people with the highest circadian variation. The increase of asthmatic status during early hours is well known single

Daily dose of inhaled corticosteroids when administered at 5:30 pm rather than 8 am nearly as effective as four doses a day.[22]

Arthritis: Rheumatoid arthritis is condition of joints pain which is distinguished from osteoarthritis as the time day when the patient's joints are more painful. Early morning stiffness occurs but symptoms are worsen in evening or afternoon.

The new generation of COX-2 inhibitor effectively relives symptoms of joints when taken in the morning but better relief is obtained in rheumatoid arthritis when part of dose is taken in evening.

Peptic ulcer: In condition of peptic ulcer or duodenal ulcer, the acid secretion occurs but due to disturb in circadian cycle the acid secretion is maximum at midnight. In peptic ulcer disease, pain and perforation of gastric and duodenal ulcer are more common at night; administration of pulsatile release containing H2-blocker drugs during the bedtime can be more effective.

Cardiovascular disease: Many severe cardiovascular events have been shows Display a highly significant circadian variation. Normally the incidence of cardiovascular events is observed mostly in early morning.[21]

Blood Pressure: Blood pressure shows the circadian variation over a 24 h period. Normally in hypertensive person blood pressure is increased in day time, low at sleeping time and again attain highest peak in morning hence increased cardiovascular accidents.[23]

Oral dosage form for drug delivery system

For oral delivery system, multiple unit dosage form offers many advantages as compared to single unit product.

1. The relative advantage of bioavailability, more consistent in blood flow levels, prediction in gastrointestinal transit time, less localized gastrointestinaldisturbances and greater safety.
2. Single unit system when admistered orally e.g. hydro dynamically balancedsystem (HBS) are more susceptible to no process and may cause variation in bioavailability and cause local irritation due to large excess of drug release at a specific site of GIT.
3. In comparison to multiple unit particulate dosage it offers advantage as single unit product as it passes uniformly throughout the GIT to avoid the vagariesof gastric empting and provide adjustable drug release.
4. The influence of gastric emptying time and intestinal motility on intra andinter- subject variation in the rate and the extent of availability can largelymodified by the use of multiple unit dosage form. It is accepted that the sizeof most of the multiparticulate enables them to pass through the constricted pyloric sphincter which make them enable to distribute themselves along the entire GI tract.[24]

Advantages of Pulsatile drug delivery system[1, 3]

(i) Improved stability of dosage form, patient comfort and patient compliance
(ii) Reduced adverse effects of drugs
(iii) Improved tolerability
(iv) Limited risk of local irritation
(v) No risk of dose dumping
(vi) Flexibility in design
(vii) Reduced dose and frequency of administration
(viii) Avoid first pass metabolism
(ix) Drug targeting to specific site
(x) Drug loss is prevented due to first pass effect.

Disadvantages of Pulsatile drug delivery system[3]

(i) Multiple formulation steps is required
(ii) Higher cost of production
(iii) Need of advance technology
(iv) Trained/skilled personal needed for manufacturing purpose.

Design of Pulsatile Drug Delivery System[25]

The main purpose of designing the dosage form by which the drug is releaseafter a lag time depends on the type of coating, polymer used, insolublepolymer coating under all physiological condition and slowly erodible coating.The rupturing of coating after a lag time is controlled by:

(i) The permeation and mechanical properties of polymer coating
(ii) The swelling behaviour of swelling polymer coating.

Timed controlled pulsatile release

(i) Single unit system
(ii) Multi-particulate system
(a) Stimuli induced Pulsatile release
(i) Thermo-responsive pulsatile release
(ii) Chemical stimuli induced pulsatile system
(b) External stimuli pulsatile release

(i) Electro responsive pulsatile release
(ii) Magnetically induced pulsatile release

Timed controlled Pulsatile Release System[13, 26, 27]

Drug release from dosage form is accordingly pre-programmed lag time.Themechanism involve here is bulk erosion of polymer through which drug release by diffusion is restricted, surface erosion of layered devices and osmotically controlled erosion coating layer. Controlled of dissolution rate of coating can be achieved by pulse drug delivery system. Pozzi et al formulated the time clock pulsatile system for oral dosage form which disintegrates the core tablet immediately after achieving the pre-determined lag time. The core tablet was made with active ingredient and bulking agent and coated with hydrophobic polymer. The optimum lag time can be achieved by altering the coating thickness. The studies concluded that in-vitro drug core dissolve immediately after direct contact with water and drug release occur within 30 minutes, this time clock approach can be used to control the onset of time. Gazzamga et al proposed the oral and colon specific drug delivery system which should programmed lag time. The prepare drug core was coated with different concentration of HPMC which act as retarding agent. In-vitro study showed a burst release immediately after the immersion of drug core and complete release was observed within 15 minute. The study concluded that the lag time is prolonged with the concentration and thickness of HPMC core.

Delivery system with soluble or erodible membranes

In this delivery system, the release of drug is controlled by dissolution and erosion of outer coating which are applied on the core drug. By optimizing the thickness of outercoating of polymer, the time dependent release of drug is obtained. The pre-determined lag time of drug release is obtained by using the various grades of HPMC layer and thickness. When this system comes in contact with aqueous fluid, the coating layer start to erode after the lag time and drug release in burst manner.

Delivery system with Repturable coating

This system is based on the mechanism of expansion of core rupturing of the coating to allow rapid drug release. These systems consist of reservoir system coated with a rupturable coating polymer. The system consist of drug containing core tablet followed a second protective layer of HPMC a gas forming agent as citric acid and sodium bicarbonate and a rupturing layer to outermost side. When these systems comes in contact with aqueous medium, the membrane rupture due to pressure developed in the system and drug release after the lag time and rupturing of membrane.

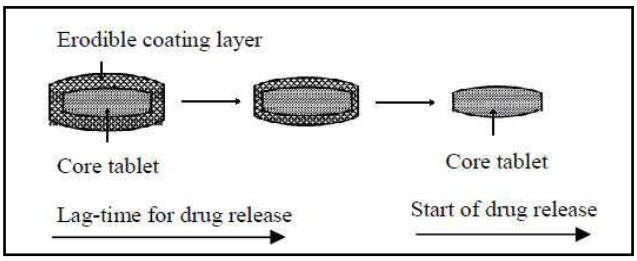

Figure 3: Repturable coating drug delivery system.[13]

Capsule based system provided with release controlling plug

These systems are based on the mechanism that lag time is controlled by plugs which are pushed by swelling or erosion off plug. Pulsinacap developed by R.P. Scherer which consists of a water-insoluble capsule enclosing drug reservoir. In these system drug core is placed in an impermeable polymeric cylinder closed with a erodible drug free plug. When this capsule system comes in contact with body fluid, the polymer swelled and after a pre-determined lag time the plug pushed itself outside the capsule system and drug release rapidly. The lag time of drug is controlled by the length of plug and insertion of plug in capsule. Polymers which are used in designing the plug based capsule system are HPMC, poly methyl acrylate, poly vinyl acetate and polyethylene oxide.

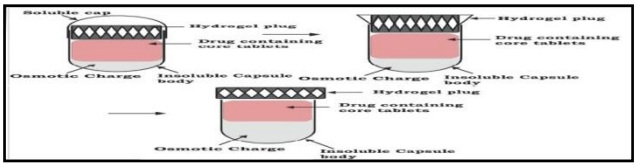

Figure 4: Capsule based system with release controlling plug[13]

Multi-particulate system[28]

These systems is based on the mechanism of change in membrane permeability, system based on soluble or eroding polymer coating and system based on rupturable coating. .Multiparticulate drug delivery are design for achieving controlled and delayed release Formulation with minimum dose dumping, achieving different release pattern and short gastric residence time. Chen developed a system which composed large number of pellets containing drug containing core, water soluble osmotic agent and water insoluble polymer film.

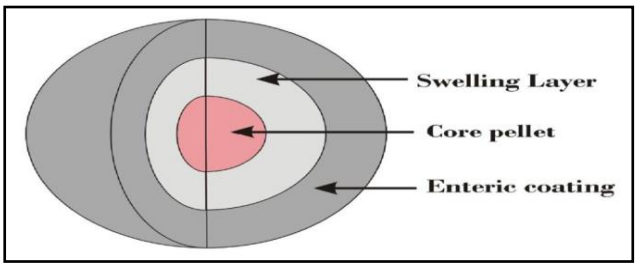

Figure 5: Multiparticulate drug delivery system[28]

Stimuli induced pulsatile release[12]

Thermo-responsive pulsatile release

These system in which polymer undergoes swelling and deswelling phase with change in Temperature which initiate the release of drug in swollen state. The release pattern of pulsatile drug release range temperature from 200^{O}c and 300^{O}c using reversible swelling properties.

Chemical stimuli induced pulsatile system

These system is based on mechanism thatdrug release occur in presence of specific chemical moieties like enzyme or proteins.

External stimuli pulsatile release system

Electro responsive pulsatile release

These systems is based on used of polymer which contains high concentration of ionisable group and pH responsive which under influence of electric field swelling and deswelling occur depending on position of hydrogel to electrode. Electrically responsive delivery systems are prepared from polyelectrolyte (polymers which contain relatively high concentration of ionisable groups along the backbone chain) and are thus, pH-responsive as well as electro-responsive. Examples of naturally occurring polymers include hyaluronic acid, chondroitin sulphate, agarose, carbomer, xanthan gum and calcium alginate. The synthetic polymers are generally acrylate and methacrylate derivatives such as partially hydrolyzed polyacrylamide, polydimethylaminopropyl acrylamide.

Magnetically induced pulsatile release

These systems contain magnetic beads in implant which upon application of magnetic field, the release of drug occur.The magnetic response is achieved by incorporation of materials like magnetite, iron, cobalt and nickel bin beads. For biomedical applications, magnetic carriers should be water-based, biocompatible, non-toxic and non- immunogenic. This approach is based on the magnetic attraction slows down the oral drugs in the gastrointestinal system which is achieved by filling an additional magnetic component into capsules or tablets. The speed of travel through the stomach and intestines can then be slowed down at specific site positions by an application of external magnet, thus changing the timing and/ or extent of drug absorption into stomach or intestines.

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