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Chrono pharmaceutical drug delivery system

V. RAVICHANDIRAN[1], V. SUBA[2], S.K. UMADEVI[3],G. JAYAVASAVI[4], J. KAUSALYA[5], T. SARASWATHY[6] and B. SENTHILNATHAN[7]*

[1-4,5]Vels college of Pharmacy, Pallavaram, Chennai (India)
[2-3]Department of Pharmacology, Vels college of Pharmacy,Pallavaram,Chennai
[6]Madras Medical College, Chennai - 3 (India).
[7]Department of Pharmaceutics, Vels college of Pharmacy (India).

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ABSTRACT

In the body under physiological conditions, many vital functions are regulated by transient release of bioactive substances at a specific time and site. Thus, to mimic the function of living systems and in view of emerging chronotherapeutic approaches, pulsatile delivery, which is meant to release a drug following programmed lag phase, has attracted increasing interest in recent years. In pursuit of pulsatile release, various design strategies have been proposed, broadly categorized into single-unit and multiple-unit systems. However, in recent pharmaceutical applications involving pulsatile delivery, multiparticulate dosage forms are gaining much favor over single-unit dosage forms because of their potential benefits like predictable gastric emptying, no risk of dose dumping, flexible release patterns and increased bioavailability with less inter- and intra-subject variability. Based on these premises, the aim of the present review is to survey the main multiparticulate pulsatile delivery systems, for which the swelling and rupturing; dissolution or erosion; and changed permeability of the coating membrane are primarily involved in the control of release. The development of low density floating multiparticulate pulsed-release dosage forms possessing gastric retention capabilities has also been addressed with increasing focus on the upcoming multiparticulate-pulsatile technologies being exploited on an industrial scale.

Key words: PDDS-Pulsatile drug delivery systems,CR-controlled release, SR-sustained release,PR-Pulsatile release,GIT-gastro intestinal tract, ER-extended release ADHD- attention deficit hyper activity disorder.

INTRODUCTION

Pulsatile system

A tool to increase therapeutic efficacy of drug.

In recent years considerable attention has been focused on the development of pulsatile drug delivery system. Delivery system with pulsatile release pattern has gained most popular form of controlled drug delivery system because conventional systems with a continuous release are not ideal. Oral controlled drug delivery systems are generally used due to convenient dosage form & it also releases drug in constant or variable rates[8,9,10]. In these system drug release generally occurs within therapeutic window for prolong period of time. Hence these systems show sustained release of drug from dosage form.

Advantages of pulsatile drug delivery system

- Extended daytime or nighttime activity
- Reduced side effects
- Reduced dosage frequency
- Reduction in dose size
- Improved patient compliance
- Lower daily cost to patient due to fewer dosage units are required by the patient in therapy.
- Drug adapts to suit circadian rhythms of body

functions or diseases.
- Drug targeting to specific site like colon.
- Protection of mucosa from irritating drugs.
- Drug loss is prevented by extensive first pass metabolism [11].

The oral controlled drug delivery system with continuous release does not show suitability in various conditions of the body which require pulsatile release of drug defined as "a pulsatile release profile" & is characterized by a time period of no release (lag time) followed by a rapid & complete drug release of drug from dosage form. Conditions requiring pulsatile release includes – A number of hormones like rennin, aldosterone & cartisole which shows daily fluctuation in their blood levels. These changes are generally known as circadian rhythm which is responsible for changes in many functions of the body like activity of liver enzyme, blood pressure, intra-ocular pressure etc [12]. PH, gastric acid secretion in stomach, gastric emptying & gastric intestinal blood transfusion [13]. Various diseases are also dependent on the circadian rhythm for example acute myocardial insufficiency occurs most commonly around 4.00 P.M. & Epileptic seizures have the highest incidence in the morning, such conditions demands consideration of diurnal progress of disease rather than maintaining constant plasma drug level. In these conditions delivery system should be administered at night but it should release drug at morning time. Some other diseases are bronchial asthma, angina pectoris, rhumatic disease, ulcer & hypertension also required time dependent delivery[14]. Drugs responsible for producing biological tolerance also require pulsatile release. These systems prevent their continuous presence at the biophase. It releases drug after lag time (time at which drug is required by the body). For drugs required to be targeted in colonic region (distal organ) the delivery system should prevent release of drug in the upper two third portions in g.i.t [15]. Drug with idiosyncratic pharmacokinetics or pharmacodynamics or drugs with extensive first pass metabolism or which show potential food interaction require pulsatile release of the drug. Some drugs induce nausea or vomiting or some cause gastric irritation or some undergo degradation in gastric acid medium, all such drug requires drug release after lag time. Pulsed fashion can be achieved by the enteric coating of delivery system .

All above conditions are required chronotherapeutics (i.e. precisely time therapy). To accomplish the objectives & advantages of chronotherapeutics, time controlled pulsatile drug delivery devices are required they show releasing the right amount at the right time.

Ideal Pulsatile Drug Delivery System

The first pulsatile drug delivery formulation, which released active substance at a precisely defined time point was formulated in the early 1990s. The aim of the research was to obtain sigmoidal release pattern. Below drug release profile is for the single pulse release system .

Classification of chrono pharmaceutical or pulsatile or time controlled system

In this review attempt is made to review various time controlled drug delivery system based on rupturing of membrane or erosion of membrane. Time dependent dosage forms are formulated to release their drug load after a predetermined lag time. Alternative terms used are pulsatile release, delayed or sigmoidal release. Besides one-pulse systems, multiple systems release the drug in subsequent pulses. The application of pulsatile release systems can be advantageous to adapt a drug therapy to chronopharmacological needs or to target a drug specific site in the gastrointestinal tract, e.g. to the colon . Lag time of 4-6 hours generally considered sufficient, since small intestine transit is about 3-4 hours, which is relatively constant. Formulation in which drug release is independent of the environmental factors like PH, enzymatic activity, intestinal motility, pressure etc. can be achieved by incorporating a lag-time into the formulation equivalent to mouth to colon transit time . The pulsatile drug delivery systems are of two types –
- Single unit system
- Multiple (pellet system) unit system

Single Unit System

Capsular system

Architecture of these systems generally consists of an insoluble capsule body housing, a drug & a plug. After a predetermined lag-time plug was removed because it undergoes swelling, erosion or dissolution. Example: pulsincap ^{R} system

– In this system a water insoluble body containing the drug formulation, system is closed with a swell able hydrogel. Plugged (insoluble but permeable & swellable) at open end . Upon contact with, gastro-intestinal fluid or dissolution medium the plug swells pushing itself out of the capsule after lag-time. Position & dimensions of plug control lag-time. For rapid release of water insoluble drug effervescent or disintegrating agents are added. No gastrointestinal irritation can be observed in both human & animal . Plug material is generally made up of following:

- Swellable materials coated with insoluble but permeable polymer (polymethacrylates)
- Erodible compressed polymer (HPMC, polyvinyl alcohol, polyethylene oxide)
- Congealed melted polymer (glyceryl monooleate)
- Enzymatically controlled erodible polymer (pectin)

Disadvantages

These systems show variable gastric residence time & this problem is overcome by enteric coating .

Pulsatile delivery by osmosis

The Port [R] system consists of gelatin shell filled with osmotically active ingredient along with drug & also having an insoluble lipidic plug. Shell is coated with semi permeable membrane (cellulose acetate) then plugged with insoluble plug as well as system comes in contact with aqueous medium the water moves across semi-permeable membrane & exert pressure which remove the plug after lag-time[30] . System shows good in-vivo & in-vitro correlation in humans & used to deliver methylphenidate to schoolage children for the treatment of attention deficit hyper activity disorder (ADHD)

Another system is also based on expendable orifice that contain capsular system in which liquid drug is absorbed on highly porous particles. Drug releases through orifice of a semipermeable capsule supported by an expending osmotic layer after the barrier layer is dissolved

Still another system is based on delivery by a series of stop. In this system the capsule

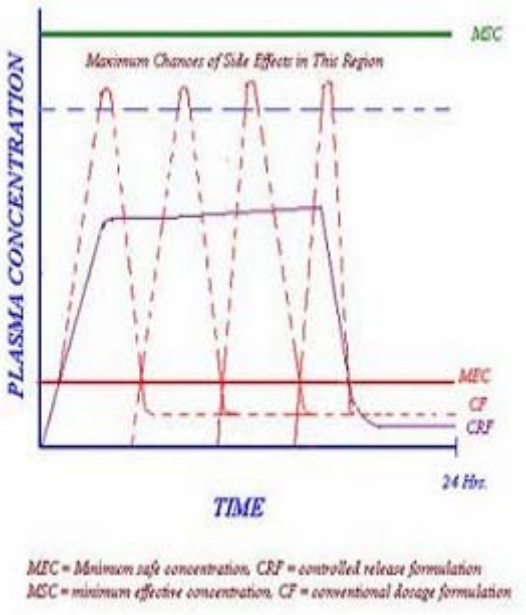

Fig. 1.

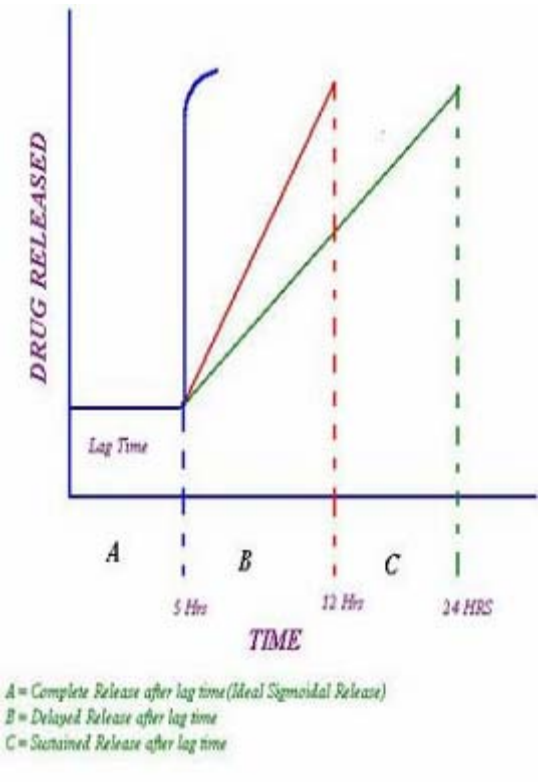

Fig. 2.

contains a drug & water absorptive water engine that are placed in compartment separated by a movable partition. These stops obstruct the movement of partition but are overcome in succession when osmotic pressure rises above threshold level

Pulsatile delivery by erosion or solublization of coating – Most of the pulsatile drug delivery systems are reservoir devices coated with a barrier layer. This barrier erodes or dissolves after specified lag period & drug is subsequently released rapidly. The lag time depends on the thickness of the coating layer . Example: The Time Clock system consists of solid dosage form coated with lipid barriers such as carnauba wax & beeswax along with surfactants like polyoxyethylene sorbitan monooleate . When this system comes in contact with the aqueous medium the coat emulsifies or erodes after the lag-time depending on the thickness of coat. The lag time of system is independent of the gastrointestinal motility, PH, enzyme & gastric residence time .

Advantage

Ease of manufacturing.

Disadvantages

In-vivo variability (food effects which is present in G.I.T.).

In another example the Chronotropic [R] system consists of solid dosage form coated with hydrophilic swellable hydroxy propyl methyl cellulose which releases drug after lag-time depending on thickness of coat & viscosity grade of hydroxypropyl methyl cellulose. The system is suitable for both tablet & capsule dosage form, both in-vivo & in-vitro lag times shows good correlation with the applied amount of the hydrophilic retarding polymer .Multi layered tablet – with the three layered tablet release pattern with two pulses was obtained, two drug layers are separated by a drug free gellable polymeric barrier layer (like HPMC, methacrylic & acrylic polymers or polyalcohols).

Pulsatile delivery by rupture of membrane

The other class of the reservoir type pulsatile system is based on rupturable coatings. The drug release from the core occurs when sorrounding polymeric membrane undergo ruptured due to inbuilt pressure within system. The effervescent excipients produces gas or osmotic agent produces osmotic pressure or swelling agent cause swelling, one of these is necessary for rupture of coating . Citric acid & sodium bicarbonate is incorporated as effervescent mixture in tablet core coated with ethyl cellulose, when system comes in contact with water it produces carbon dioxide gas which exerts pressure & after lag time rupture the membrane & rapid release of drug occurs. A reservoir system with a semi permeable coating is proposed especially with drugs with high first pass effect in order to obtain in-vivo drug pattern similar to the administration of several immediate release doses croscarmellose sodium starch glycollate or low substituted hydroxy propyl cellulose were used as swelling substances, which resulted in complete film rupture followed by rapid drug release. The lag time is controlled by composition of outer polymeric membrane (HPMC water soluble polymer increased permeability decreased lag-time).

Multiparticulate System

Multiparticulate systems are reservoir type of devices with a coating, which either ruptures or changes its permeability. Drug is coated over sugar seeds these granules may then be packaged in a capsule or compressed with additional excipients to form a tablet. The active pharmaceutical ingredient may also be blended or granulated with polymers before coating to provide an additional level of control. However, drug loading in this type of system is low due to higher need of excipients

These systems show various advantages over single unit systems, which includes –

- Short gastric residence time
- Reproducible gastric residence time
- No risk of dose dumping
- Flexible to blend pellets with different composition or release pattern
- Lowest transit time variability
- Unique profiles
- Amenable to capsule & tablets
- Capable of pulsatile release

Disadvantages

- Multiple manufacturing steps
- Low drug load
- Incomplete release

Pulsatile release by rupturing of membrane

In these multiparticulate system drug is coated on sugar seeds & then coated with insoluble & swellable top layer . The swelling agent includes superdisintegrents like carboxy methylcellulose, sodium starch glycollate, L-hydroxy propyl cellulose. Polymers like polyacrylic acid, polyethylene glycol etc. alternatively comprising of a mixture of tartaric acid & sodium bicarbonate that used as effervescent agent. Water ingress to system causes the coating to swell, rupture & release of drug occurs. Release of drug is independent of pH or solubility of drug. Lag-time can be varied by varying thickness of coating or by changing amount of plasticizers in the outermost layer. If concentration of osmotic agent increases rapid release of drug after lag-time can be observed. In-vivo studies of time controlled explosion system with an in-vitro lag-time of three hours showed appearance of drug in blood after 3 hours, and maximum level after 5 hours .

Rupturable coating with osmosis

These system contains core having drug (low bulk density solid or liquid lipid material) & disintegrant. Core is coated with cellulose acetate polymer. System is combination of swelling & osmotic effect, upon immersion in aqueous medium, water penetrates the core, displaces the lipid material, after depletion of lipid material internal pressure increases until a critical stress is reached, which causes rupture of coating .

Another type of system is one in which tablet or capsule is composed of large number of pellets (two or more pellets) . Single pellet of this system contains drug plus osmotic agent & coated with water permeable, water insoluble polymer. In film hydrophobic agent (water insoluble) is incorporated which alters permeability. The rate of water influx & drug efflux causes the film coating of each population to differ from any other pellet coating in the dosage form. Pellet gets swelled due to dissolution of osmotic agent as it comes in contact with water resulting in regulation of diffusion & release of drug content from pellet. Each pellet population of system shows this effect. The coating thickness may vary & this system is used for antihypertensive drug diltiazem. Osmotically active compound don't undergo swelling, the use of osmotic active agent was reported by Shultz & Kleinbudde . The pellet core made up of drug, sodium chloride & coated with semipermeable cellulose acetate polymer (permeable to water & not to drug). Varying thickness of coating & amount of plasticizer in coating can vary lag-time of system. Sodium chloride provides fast release of drug if it is absent in core then a sustained release was observed after lag-time due to lower degree of swelling & generation of small fissures in core. Chen has also reported a system-containing core of drug & osmotically active agent coated with insoluble permeable membrane.

Change in membrane permeability based pulsatile release

The permeability & water uptake of acrylic polymers with quaternary ammonium groups can be influenced by the presence of different counter ions . Several delivery system with sigmoidal or pulsatile release based on these ion exchange have been developed Eudragit RS 30D is polymer of choice, it contains positively polarized quaternary ammonium group in the polymer side chain & also negative hydro chloride counter ions. The ammonium group is hydrophilic causes interaction with water & changes in permeability of it in controlled manner. In these system core containing drug & sodium acetate coated with four different layer of Eudragit RS30D. Small amount of sodium acetate dramatically change the permeability of eudragit film. After lagtime permeability increases due to increase in interaction between eudragit & acetate, resulting in entire drug release within few minutes. Increase in lag-time occurs as thickness increases but it has no effect on release .

Sigmoidal release system consists of drug & succinic acid core coated with ammonio-methacrylate copolymer USP/NF TYPE B. The lag-time is controlled by the rate of water influx through polymer membrane. Succinic acid dissolves by the water causes increase in permeability of hydrated polymer film that increases free volume. These findings were used to design acid containing core that is coated by polymeric membrane.

CONCLUSION

Successful colonic delivery can be obtained by pulsatile system for drugs with a high

first pass effect, requiring dosing hora somni, site specific absorption & showing chronopharmacological behaviour. A number of formulations with single & multiple unit systems have been designed in recent past but most lack the site specificity. Therefore, there is a need to comprehend the effect of the biological environment on release performance so that a successful design with expected in vivo performance can be developed.

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