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Review Article

Novel Concept of Drug Delivery Based on Chronotherapy: A Review

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ABSTRACT

Chronotropic drug delivery systems are drawing an increasing interest of the galvanic research in the field of pharmaceuticals towards the development of more efficacious drug delivery systems for such diseases which pertains to a well established oscillatory rhythm in their pathogenesis including hypertension, angina, asthma, cancer, arthritis, allergic rhinitis, attention deficit syndrome, hypercholestremia, diabetes and many others. Currently, various approaches viz., single unit, multiparticulate systems, electro-responsive pulsatile release, magnetically induced pulsatile release, systems with different type of polymeric barrier coatings, stimuli sensitive etc. has been so far developed and characterized successfully. Based on above approaches, recently novel formulations viz., Pulsincap™, TIMER$_x$, CONTIN, OROS, CODAS, DIFFUCAPS, CEFORM, etc. have also been envisaged by various researchers extensively. Pulsatile drug delivery systems involve spatial and temporal release of the drug molecules after a predetermined lag time period. Sigmoid release profile can be followed by these systems, which leads to maximisation of therapeutic effect and rapid drug release. The article on the whole summarises the efficiency of such systems for diseases requiring safer, potential and holistic approaches respectively.

Keywords: Circadian rhythm, Chronotherapy, Bioerodable systems, Pulsatile drug delivery, Electro-responsive system.

INTRODUCTION

Chronotropic drug delivery systems have drawn an increasing interest over the last few decades due to the advancement of technologies in the pharmaceutical field. Currently the emphasis of galvanic research is turned towards the development of more efficacious drug delivery system while using the existing drug or molecules rather than going for new drug discovery and development process. Drug regimen based on circadian rhythm is recently gaining much attention for treatment of various diseases such as asthma, hypertension, arthritis, diabetes, etc. with better patient compliances.

Chronotherapeutics is the clinical practice of synchronizing drug delivery in a manner consistent with the body's circadian rhythm to produce maximum drug effect or decrease undesirable side effects. Pulsatile drug delivery system is the time and site specific drug delivery systems, involving transient release of sufficient amount molecules within a short time period.The chronotherapy have several advantages like

- Controlled drug release, hence assuring effective management of certain diseased conditions.
- Can evaluate the effectiveness of the new strategies with current approach of treatment.
- It gives you a period to psychologically to the new schedule.
- Increased patient compliances.

Ideal Characteristics of Chronotherapeutics drug delivery systems

- It is non-toxic within approved limits of use
- It is having a real time and specific triggering biomarker for a given disease state
- It has a feedback control system
- Easy to manufacture at economic cost
- Easy to administer in patients in order to enhance compliance to dosage regimn.

Chronotherapy based system represents the most efficacious form of delivery systems as the drug release through them follows a sustained order pattern. Activities showing circadian variation demands timely scheduled drug release for effective drug action, e.g. inflammation associated with morning body stiffness. Asthma is one of the diseases where pulsatile drug delivery system can be useful. Circadian changes are seen in normal lung function which reaches a low point in the early morning hours. In cardiovascular disease, several functions, e.g. Blood pressure, heart rate, stroke volume, cardiac output and blood flow to the cardiovascular system is subjected to circadian rhythm.

Pulsatile drug delivery system are designed in such a manner that the drug release through such systems occurs after a predetermined off release period, i.e., lag time. These systems are beneficial for the drugs where a night time dosing is required and which have a high first-pass effect or a specific site of absorption in GIT. Pulsatile drug delivery systems are gaining a lot of interest and attention these days. 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." Though most delivery systems are designed for constant drug release over a prolonged period of time, pulsatile delivery systems are characterized by a programmed drug release, as constant blood levels of a drug may not always be desirable. Pulsatile systems are designed in a manner that the drug is available at the site of action at the right time in the right amount.

CLASSIFICATION OF PDDS

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

1. Timely modulated pulsatile release

I. Single unit system

II. Multi-particulate system

2. Stimuli actuated pulsatile release

I. Thermo-Responsive Pulsatile release
II. Chemo-Responsive Pulsatile systems
III. Electro- Responsive Pulsatile release
IV. Magnetically induced Pulsatile release

I. Single unit systems

i. Capsular Systems

Such systems consist of an insoluble capsule body housing a drug and a plug. The plug is removed after a pre-determined time lag due to swelling, erosion, or dissolution. The body is closed at the open end with a swellable hydrogel plug. After contact with dissolution medium or gastro-intestinal fluids, the plug swells, pushing itself out of the capsule after a time lag which is followed by an instantaneous release of the drug. The Pulsincap system is an example of such a system that is made up of a water-insoluble capsule body filled with drug formulation. The time lag can be controlled by changing the dimension and the position of the plug. For water insoluble drugs, a instantaneous release can be ensured by inclusion of effervescent agents or disintegrants. The plug material consists of insoluble but permeable and swellable polymers (e.g.: polymethacrylates) erodible compressed polymers (e.g.: hydroxyl propyl methyl cellulose, polyvinyl alcohol, polyethylene oxide), congealed melted polymers (e.g.: saturated polyglycolated glycerides, glycerylmonoole and enzymatically controlled erodible polymer e.g.: pectin). These formulations are well tolerated in animals and healthy volunteers, and there have been no reports of gastro-intestinal irritation. However, there was a potential problem of variable gastric residence time, which was overcome by enteric coating the system to allow its dissolution only in the higher pH region of small intestine.

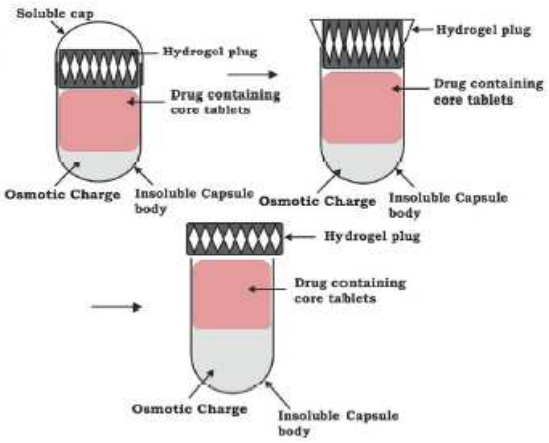

Figure 1 The Capsular System

ii. Port systems

The Port System - consists of a gelatin capsule and in which gelatin capsule coated with a semi permeable membrane (e.g.: cellulose acetate) housing an insoluble plug (e.g.: lipidic) and an osmotically active agent along with the drug formulation. When it comes in contact with the aqueous medium, water diffuses across the semi permeable membrane, resulting in increased inner pressure that ejects the plug after a – time lag. The time lag is controlled by the thickness of semi permeable membrane. The system showed good correlation in lag times of in-vitro and in vivo experiments in humans.

An osmotically driven capsular system was developed for delivering of drug in liquid form. In this system, liquid drug is absorbed into highly porous particles, which release the drug through an orifice of a semi permeable capsule supported by an expanding osmotic layer after the barrier layer is dissolved. The capsular system delivers drug by the capsule's osmotic infusion of moisture from the body. The capsule wall is made up of an elastic material and possesses an orifice. As the osmosis proceeds, the pressure within the capsule rises, causing the wall to stretch.

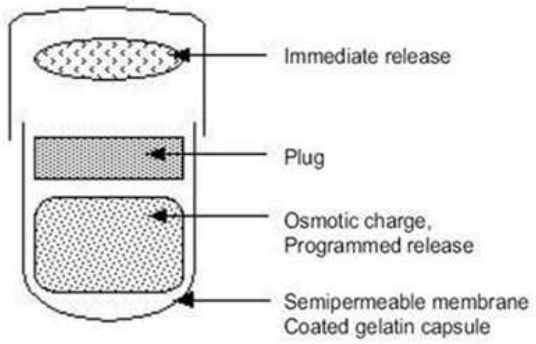

Figure 2 The Port System

iii. Delivery by a series of stops

This system is employed for implantable capsules. The capsule contains a drug and a water absorptive osmotic engine that are placed in compartments separated by a movable partition. The pulsatile delivery is achieved by a series of stops along the inner wall of the capsule. These stops obstruct the movement of the partition but are overcome in succession as the osmotic pressure rises above a threshold level. The number of stops and the longitudinal placements of the stops along the length of the capsule dictate the number and frequency of the pulses, and the configuration of the partition controls the pulse intensity.

iv. Delivery by solubility modulation

These systems contain a solubility modulator for pulsed delivery of a number of drugs. The system was mainly developed for delivery of salbutamol sulphate. The composition contains the drug (salbutamol sulphate) and a modulating agent, sodium chloride (NaCl). The amount of NaCl was such that it was less than the amount needed to maintain saturation in a fluid that enters the osmotic device. The pulsed delivery is based on drug solubility. Salbutamol has solubility of 275 mg/ml in water and 16 mg/ml in saturated solution of NaCl, while NaCl has solubility of 321 mg/ml in water, and its saturation solubility is 320 mg/ml. These values show that the solubility of the drug is a function of the modulator concentration, while the modulators solubility is largely independent of drug concentration. The modulating agent can be a solid organic acid, inorganic salt, or organic salt.

v. Delivery by reservoir systems with erodible or soluble barrier coatings

Most of the pulsatile drug delivery systems are reservoir devices coated with a barrier layer. This barrier erodes or dissolves after a specific lag period, and the drug is subsequently released rapidly. The time lag depends on the thickness of the coating layer.

The Time Clock system consists of a solid dosage form coated with lipid barriers containing carnauba wax and bees wax along with surfactants, such as polyoxyethylene sorbitan monooleate. This coat erodes or emulsifies in the aqueous environment in a time proportional to the thickness of the film, and the core is then available for dispersion. The major advantage of this system is its ease of manufacture without any need of special equipment. The disadvantage of this system is a premature drug release when the penetrating water dissolves the drug. The Chronotropic system consists of a drug-containing core coated by hydrophilic swellable hydroxypropylmethyl cellulose (HPMC), which is responsible for a lag phase in the onset of drug release. Time lag is controlled by the thickness and the viscosity grades of HPMC used in coating the drug core. The system is suitable for both tablets and capsule formulations.

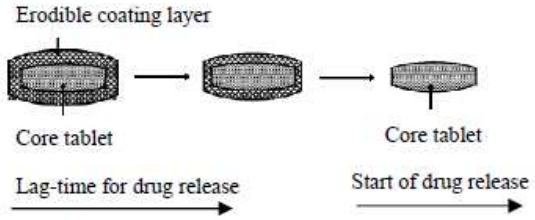

Figure 3 Drug Release Through Reservoir Systems

II. Multiparticulate Systems

Multi-particulate drug delivery systems are mainly oral dosage forms consisting of a multiplicity of small discrete units, in which the active substance is present as a number of small independent subunits. They provide many advantages over single-unit systems because of their small size, less inter and intra-subject variability in gastrointestinal transit time, reduced adverse effects and improved tolerability, no risk of dose dumping, flexibility in design and finally Improve stability However, there are some draw backs in this system, which include lack of manufacturing reproducibility, high cost of production, multiple formulation steps and also the need of advanced technologies. There are different types of multiparticulate systems and these are enumerated and explained below:

i. Pulsatile System Based on Rupturable Coating

This is a multiparticulate system in which drug is coated on non-pareil sugar seeds followed by a swellable layer and an insoluble top layer. The swelling agents used include superdisintegrants like sodium carboxymethyl cellulose, sodium starch glycollate, L hydroxypropyl cellulose, etc. Upon ingress of water, the swellable layer expands, resulting in rupture of film with subsequent rapid drug release. The release is independent of environmental factors like pH and drug solubility. The lag time can be varied by varying coating thickness or adding high amounts of lipophilic plasticizer in the outermost layer.

ii. Time controlled expulsion systems

This system is based on a combination of osmotic and swelling effects. The core contains the drug, a low bulk density solid and/or liquid lipid material (e.g., mineral oil) and a disintegrant. The core is further coated with cellulose acetate. Upon immersion in aqueous medium, water penetrates the core displacing the lipid material. After the depletion of lipid material, internal pressure increases until a critical stress is reached, which results in rupture of the coating material. Another system is based on a capsule or tablet composed of a large number of pellets consisting of two or more pellets or part.

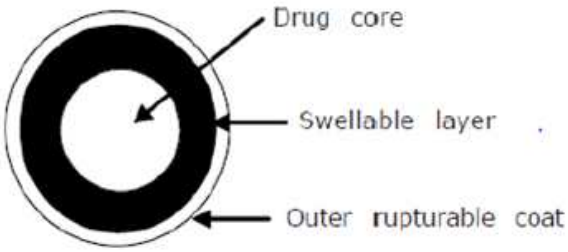

Figure 4 Reservoir systems with rupturable coating layer

iii. Pulsatile Delivery by Change in Membrane Permeability

The permeability and water uptake of acrylic polymers with quaternary ammonium groups can be influenced by the presence of different counter-ions in the medium. Several delivery systems based on this ion exchange have been developed. Eudragit RS 30D is reported to be a polymer of choice for this purpose. It typically contains positively polarized quaternary ammonium group in the polymer side chain, which is always accompanied by negative hydrochloride counter-ions. The ammonium group being hydrophilic it facilitates the interaction of polymer with water, thereby changing its permeability and allowing water to permeate the active core in a controlled manner.

iv. Sigmoidal Release Systems

This consists of pellet cores comprising drug and succinic acid coated with ammonium methacrylate copolymer USP/NF type B. The time lag is controlled by the rate of water influx through the polymer membrane. The water dissolves acid and the drug in the core. The acid solution in turn increases permeability of the hydrated polymer film. The different types of acids that can be used include succinic acid, acetic acid, glutaric acid, tartaric acid, malic acid, or citric acid.

v. Low density floating multiparticulate pulsatile systems

Conventional multiparticulate pulsatile release dosage forms mentioned above are having longer residence time in the gastrointestinal tract and due to highly variable nature of gastric emptying process may result in vivo variability and bioavailability problems. In contrary, low density floating multiparticulate pulsatile dosage forms reside only in stomach and not affected by variability of pH, local environment or gastric emptying rate. These dosage forms are also specifically advantageous for drugs either absorbed from the stomach or requiring local delivery in stomach.

2. Stimuli induced pulsatile release system

Several polymeric delivery systems undergo phase transitions and demonstrate marked swelling-deswelling changes in response to environmental changes including solvent composition, ionic strength, temperature, electric fields, and light. Responsive drug release from those systems results from the stimuli-induced changes in the gels or in the micelles, which may deswell, swell, or erode in response to the respective stimuli. The mechanisms of drug release include ejection of the drug from the gel as the fluid phase synergies out, drug diffusion along a concentration

gradient, electrophoresis of charged drugs towards an oppositely charged electrode and liberation of the entrapped drug as the gel or micelle complex erodes.

Chemical stimuli induced pulsatile systems

i. Glucose-responsive insulin release devices

A rhythmic increase in the levels of glucose in the body occurs during Diabetes Mellitus, provoking the administration of insulin at an appropriate time. Various systems have been developed which are able to respond to changes in glucose concentration. An example of 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 stimulates 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 the insulin release. Examples of the pH sensitive polymers include N, N dimethylaminoethyl methacrylate, chitosan, polyol etc.

ii. Inflammation-induced pulsatile release

On receiving any physical or chemical stress, such as injury, fracture etc., inflammation take place at the injured sites. During inflammation, hydroxyl radicals are produced from these inflammation-responsive cells. Degradation via hydroxyl radicals however, is usually dominant and rapid when Hyaluronic Acid gel is injected at inflammatory sites. Thus, it is possible to treat patients with inflammatory diseases like rheumatoid arthritis; using anti inflammatory drug incorporated HA gels as new implantable drug delivery systems.

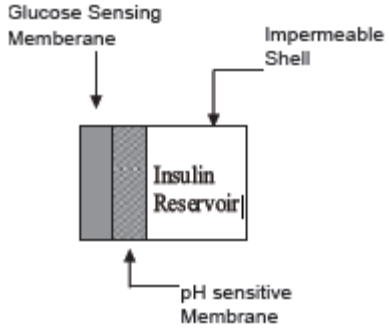

Figure 5 Schematic diagram of a glucose sensitive dual membrane system

iii. Drug release from intelligent gels responding to antibody concentration

There are numerous kinds of bioactive compounds which exist in the body. Recently, novel gels were developed which responded to the change in concentration of bioactive compounds to alter their swelling/deswelling characteristics. Special attention was given to antigen antibody complex formation as the cross-linking units in the gel, since such interaction is very specific. Utilizing the difference in association constants between polymerized antibodies and naturally derived antibodies towards specific antigens, reversible gel swelling/deswelling and drug permeation changes occurs.

iv. pH sensitive drug delivery systems

pH sensitive drug delivery systems comprises of two components, one being the fast release type , and the other involving pulsed release which releases the drug in response to alteration in the pH. Proper selection of pH dependent polymers, aids in drug release at specific location of gastrointestinal tract. Examples of pH dependent polymers include cellulose acetate phthalate, polyacrylates, Eudragits, sodium carboxymethylcellulose. These polymers are used as enteric coating materials so as to provide release of drug in the small intestine.

Recent Advanced Technologies for Chronotherapeutics

- CONTIN TECHNOLOGY: This technology provides for closer control over the amount of drug released to the blood stream and benefits patients in terms of reducing the number of doses.
- OROS TECHNOLOGY: Chonoset is proprietary OROS delivery system that reproducibly delivers a bolus drug dose, in time or site specific manner, to the gastrointestinal tract.
- CODAS TECHNOLOGY: It is a multiparticulate system which is designed for bedtime drug dosing, incorporating a 4-5 hrs delay in drug delivery.
- CEFORM TECHNOLOGY: This technology allows for the production of uniformly sized and shaped microspheres of pharmaceutical compounds.
- DIFFUCAPS TECHNOLOGY: DIFFUCAPS technology is a versatile approach for chronotherapy for delivering drugs into the body in a circadian release fashion.
- CHRONOMODULATING INFUSION PUMPS: These systems contains core having drug (low bulk density solid or liquid lipid material) and disintegrant. These pumps have been effectively used in the chronotherapy of several diseases such as cancer and diabetes.
- TIMERx TECHNOLOGY: This system can precisely control the release of the active drug substance in a tablet by varying the proportion of gums, together with the third component, the tablet coating and the tablet manufacturing process.
- PULSYS: It comprises of three components: one immediate release and two delayed release by using soluble and insoluble coating materials.
- PORT TECHNOLOGY: The programmable oral release technologies system is uniquely coated, encapsulated system that can provide multiple programmed release of the drug.
- EGALET TECHNOLOGY: It is a delayed release form consisting of an impermeable shell with two lag plugs, enclosing a plug of active drug in the middle of the unit.
- CONTROLLED RELEASE MICROCHIPS: This is an alternative method to achieve pulsatile release using microfabrication technology.
- THREE DIMENSIONAL PRINTING: Three dimensional printing is a novel technique used in the fabrication of oral dosage delivery pharmaceuticals based on solid freeform fabrication methods.

Future Prospectives of Chronotherapeutic - Pulsatile Delivery Systems

Can chronotherapeutic drug delivery systems change the tide for controlled release drug products in the market? The answer to the question is probably yes. Intensive

research is going on in this field to outrage the conventional formulations for better therapeutic treatment of the diseases which are dependent on the circadian rhythm. These systems from improving patient compliance to decreasing the dosing frequency offer a number of advantages. Significant progress have been made and still further stimulation of experimental and clinical research is required to acquire full fledge benefits from such systems.

REFERENCES

1. B. Lemmer, Chronobiology, drug-delivery and chronotherapeutics, Adv. Drug Deliv. Rev. 59 (2007) 825–827.
2. Evans RM, Marain C, et al, editors.eds. Taking Your Medication: A Question of Timing Chicago, IL: American Medical Association; **1996**. pp 3-8.
3. B.C. Youan, Chronopharmaceutical drug delivery systems: Hurdles hype or hope? Adv. Drug Deliv. Rev. 62 (2010) 898–903.
4. G. D. Rosenberg, D. J. Simmons, Rhythmic dentinogenesis in the rabbit incisor: circadian, ultradian and infradian periods, Calcified Tissue Int. 32 (2006) 29–44.
5. T. Bussemer, I. Otto, R. Bodmeier, Pulsatile drug-delivery systems, *Crit. Rev. Ther. DrugCarrier Sys*t. **2001**; 18: 433 – 458.
6. H. Kitano, Systems biology: a brief overview, *Science* **2002**; 295: 1662 – 1664.
7. Pozzi F., Furlani P., Gazzaniga A., Davis S.S, Wilding I.R., “The time clock system: a new oral dosage form for fast and complete release of drug after a predetermined lag time”, J. Controlled Release 31, 1994, 99-10.
8. Makhija N. Sapna, Vavia R Pradeep, Controlled porosity osmotic pump based controlled release system of pseudoephedrine, Cont. J. Rel. 2003,p.5-18.
9. Nagar Mayank, Singhai Sanjay, Chopra V.S., Gautam Namrata, Trivedi Piyush, Chronotropic systems: An emerging trend in drug delivery for pulsed release in Chronopharmacotherapy, Int.J.Pharm Clin. Res., 2010, Vol 2(1) p. 10-19.
10. Okimoto Kazuto, Ohike Atsuo, Ibuki Rinta , Aoki Osamu, Ohnishi Norio, Rajewski A. Roger, Stella J Valentino, Irie Tetsumi, Uekama Kaneto , Cont. J. Rel., 1999,p. 311-319.
11. Patel C. Dhirendra , Patel B. Ritesh, Patel B Gargi, Pulsatile drug delivery system , Int. J. Pharm. Res. Sci.2012,Vol.1(5),p.277-296.
12. Prabakaran D, Singh Paramjit, Kanaujia Parijat, Vyas P Suresh, Effect of hydrophilic polymer on the release of dilitazem hydrochloride from elementary osmotic pump, Int. J. Pharm. 2003, 259,p.173-179.
13. Rasve Ganesh, Borade Ganesh, Deshmukh Siddheshwar, Tagalpallewar Amol, Pulsatile drug delivery system current scenario, Int. J. Pharm. Biosci.,2011, Vol 2(3).
14. Sharma G.S, M.V Srikanth, M.V Uhumwangho, K.S Phanikumar, K.V Ramanamurthy, Recent trends in pulsatile drug delivery systems : A Review, Int.J. Drug Del. 2012, Vol2 p. 200-212.
15. Jain Deepika, Raturi Richa, Jain Vikas, Bansal Pravin, Singh Ranjit, Recent technologies in pulsatile drug delivery systems, Landes Bioscience, 2011, Vol1(1).
16. Abdelkader Hamdey, Ossama Youssef Abdalla, Hesham Salem, Formulation of controlled release baclofenac matrix tablets: Influence of some hydrophilic polymers on the release rate and in vivo evaluation, AAPS Pharm.Sci.Tech 2007, Vol 8 (4) article 100.
17. Choudhary P., Panigrahi T, Tripathy N, Behera S, Novel approaches and development in colon specific drug delivery system: A Review, Webmed Central Pharm. Sci. 2012, Vol 3(2).
18. Guan Jin , Zhou Liying, Nie Shufang, Yan Tingxu, Tang Xin, Pan Weisan, A novel gastric resident osmotic pump tablet : in vitro and in vivo evaluation ,Int J Pharm 2010 ; 383 , p. 30-60.