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A REVIEW: PULSATILE DRUG DELIVERY SYSTEM

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ABSTRACT

In the recent times the focus is more on the development of effective drug delivery systems rather than the development of new drug molecules. Pulsatile drug delivery ensures a right dose at right time at right place. It shows a sigmoid drug release with a lag time. After the lag time the drug is released rapidly and completely at a certain time or place. Pulsatile drug delivery delivers the drug at a particular time which is needed for the diseases which exhibit circadian rhythm and for the drugs which show high first pass metabolism, gastric irritation or for local effect. Several diseases such as asthma, cardiovascular diseases, peptic ulcers which follow the circadian rhythm can be treated by Pulsatile drug delivery. It has many advantages like decreased dose, minimum side effects and increased patient compliance. There are many systems like single unit, multiple unit and stimuli induced systems. Several Pulsatile drug delivery technologies are discussed in the article.

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INTRODUCTION

Drug delivery systems have drawn increasing interest over the past few decades with the advancement of technology in the pharmaceutical industry. Nowadays, the focus of pharmaceutical research is on creating more effective drug delivery systems with existing molecules rather than new drug development due to the complications built in.

Several research experiments are ongoing worldwide for the development of new drug delivery systems. The conventional immediate release dosage forms have many disadvantages like increased frequency of administration, larger dose required and more side effects. These are overcome by the controlled and sustained release dosage forms. Nonetheless these are not suitable for the diseases which show circadian rhythms.

Pulsatile system accomplished this requirement. The system consists of a lag time during which the drug is not released. After the specific pre determined lag time the drug is released at a particular time after administration. These are fabricated to achieve the time specific and site specific drug delivery[1].

CHRONOTHERAPEUTICS

'Chronopharmaceutics' is made up of two words Chronobiology and Pharmaceutics. Chronobiology is the study of biological rhythms and their mechanisms. The biological rhythms are of following types:

Ultradian rhythms: More than one cycle per day

Circadian rhythm: One cycle per day

Infradian rhythm: Less than one cycle per day.

Chronopharmaceutics is the branch of pharmaceutics that concern with the drug delivery systems which releases the drug according to the biological rhythm of the disease [2]. The diseases which require the Chronotherapeutic drug delivery include mentioned in Table no: 1.

Table.no 1: Diseases requiring pulsatile drug delivery.

Disease	Chronological behaviour	Drugs used
Arthritis	Pain in the morning and more pain at night	NSAIDS, Glucocorticoids
Asthma	Precipitation of attacks is during night or early morning hour	Antihistamines, β2 agonist
Attention deficit syndrome	Increase in DOPA level in afternoon	Methylphenidate
Cardiovascular diseases	BP is at its lowest during the sleep cycle and rises steeply during early morning awakening period	Calcium channel blockers, ACE inhibitors, Nitroglycerin
Diabetes mellitus	Increase in the blood sugar level after the meal	Sulphonyl urea, insulin, biguanide
Hyper cholesterolemia	Cholesterol synthesis is high during night than the during day time	HMG CoA reductase inhibitors
Peptic ulcer	Acid secretion is high in afternoon and at night	H2 blockers

Advantages:

1. It is possible to use these devices for prolonged daytime or nighttimes activities.
2. We increasing the dose rate, dose length, and cost, thereby reducing side effects, thereby enhancing adherence with patients.
3. Hormones like renin, aldosterone, and cortisol etc. will alter their blood levels with circadian rhythms, so drug delivery through this process matches circadian body pleasant rhythms.
4. It is possible to achieve drug targeting to a specific site, such as the colon (in the case of ulcerative colitis).
5. This process helps to prevent the continued presence of certain medications that create biological resistance (e.g. salbutamol sulphate) and thus improve their therapeutic effect.
6. These systems are useful for drugs with chronopharmacological behaviour, where dosage is necessary at night
7. We have steady concentrations of drugs at the site of action and prevent variations in the peak valley.
8. Protection from the stomach environment is important for drugs that cause stomach inflammation (e.g. NSAIDS) or deterioration in the stomach medium (e.g. peptide drugs) so that the best option can be enteric coated Pulsatile drug delivery system [3].

Disadvantages:

1. High dose of medication required
2. Proportionally higher requirement of excipient
3. Failure to reproduce manufacturing and efficacy
4. Large number of process variables
5. Multiple stages of formulation
6. Higher production costs
7. Requirement of advanced technology
8. Trained / skilled manufacturing workers required[4].

NEED FOR PULSATILE DRUG DELIVERY SYSTEM

Pulsatile release is applicable to the conditions where controlled and sustained release is not suitable.

1. First pass metabolism: Many medications, including beta blockers and salicylamide, undergo extensive first pass metabolism and allow fast feedback of drugs to saturate metabolizing enzymes to reduce pre-systemic metabolism. A constant / sustained oral delivery method would therefore lead to reduced oral bioavailability.
2. Biological tolerance: Drug plasma profiles often accompanied with the decreased pharmacotherapeutic effect of drug.
3. Special chronopharmacological needs: Several diseases and symptoms persue circadian rhythms. Hence it requires the drug release at a particular time. E.g. Asthma, Arthritis e.t.c.,
4. Local therapeutic need: Diseases such as inflammatory bowel disease and local infections in the GIT require local therapeutic effect.
5. Gastric irritation and drug instability in gastric fluids: Some drugs require the protection from the gastric environment which undergoes degradation in the gastric Ph(e.g., Peptide drugs), irritates the stomach (e.g., NSAID'S)[5].

CLASSIFICATION

TIME CONTROLLED PULSATILE RELEASE

Single unit system

- Capsular Systems
- Capsular System Based on Osmosis
- Pulsatile system with erodible or soluble barrier coating
- Pulsatile system with rupturable coatings

Multiple unit system

- Pulsatile system based on rupturable coating
- Osmatic-based rupturable coating
- Pusatile delivery by change in membrane permeability
- Sigmoidal release system
- Low density floating multi particulate system

INTERNAL STIMULI INDUCED SYSTEM

- Temprature – induced pulsatile release
  - Thermoresponsive hydrogel systems
  - Thermoresponsive polymer micelle system
- Glucose responsive insulin release devices
- Ph sensitive drug delivery system
- Inflammation – induced pulsatile release
- Enzmatically-activated liposomes

III. EXTERNAL STIMULI INDUCED SYSTEM

- Magnetically induced system
- Ultrasound induces system
- Electric field induces system
- Light induces system

TIME CONTROLLED PULSATILE RELEASE

Single unit system

Capsular Systems

This consists of a water insoluble capsule body filled with drug formulation. The capsule body at the open end is closed with a swellable hydrogel plug. When the capsule comes in contact with the GI fluids, the plug swells and after a lag time, pushes itself out of the capsule which leads to drug release as a pulse. The lag time depends on the dimensions and the position of the plug. The plug material consists of insoluble but permeable and soluble polymers, e.g. Polymethacrylates, congealed melted polymers, eg. Glyceryl monooleate, erodible compressed polymers, e.g. HPMC, enzymatically controlled erodible polymers, e.g. Agar, pectin

Capsular System Based On Osmosis(Port System):

The system was developed by Therapeutic system research laboratory Ann Arbor, Michigan, USA. This system consists of a capsule coated with a semi permeable membrane (cellulose acetate). The capsule contains an insoluble plug, an osmotically active agent and drug formulation. When the capsule comes into contact with GI fluids, water diffuses through the semi permeable membrane, resulting in increased pressure inside that ejects the plug after a predetermined lag time. The lag time is controlled by the thickness of the coating.

Pulsatile System With Erodible Or Soluble Barrier Coating:

The pulsatile drug delivery systems consist of drug reservoir with polymer coating. This barrier coating erodes or dissolves after a specific lag period, and leads to the rapid release of drug. The lag time depends on the thickness of the coating layer. The coating layer is dipodic barrier containing carnauba wax and bees wax along with surfactants (spans). After a lag time the coat erodes or emulsifies in the aqueous environment and then the drug is dispersed in the GIT[6].

Pulsatile System With Rupturable Coatings:

This includes the reservoir of drug coated with the insoluble polymer. The drug is released by the rupturing of the coating polymer which is due to the effervescent action of the components incorporated into the core tablet. The effervescent agent include the citric acid and sodium bicarbonate which are incorporated in the core tablet when comes in contact with the GI fluids release the CO2 gas that leads to rupturing of the coating. A semi permeable coating can be used for the drugs having high first pass metabolism to have drug release patterns similar to the immediate release dosage forms[7].

MULTI-PARTICULATE SYSTEM

Pulsatile System Based On Rupturable Coating:

In this technique the sugar beads coated with the drug layer followed by the polymer coating. The insoluble swellable polymers and includes superdisintegrants like sodium carboxymethyl cellulose, sodium starch glycolate, L-hydroxypropyl cellulose, etc., When these are ingested the polymer coating swells and ruptures leads to the pulsed release of the drug. The lag time can be varied by the thickness of the polymer coating or adding high amounts of plasticizer in the coated polymer layer[8].

Osmotic-Based Rupturable Coating Systems:

This system involves both osmotic and swelling effect. The core containing the drug, a low bulk density solid and/or liquid lipid material (eg, mineral oil) and a disintegrant was prepared. This core was then coated with cellulose acetate. Upon immersion in aqueous medium, water penetrates the core displacing lipid material. After the depletion of lipid material, internal pressure increases until a critical stress is reached, which results in rupture of coating. The use of osmotically active agents that do not undergo swelling was reported by Schultz and Kleinebudde

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[9].

Sigmoidal Release System:

This system consists of pellet cores comprising drug and succinic acid coated with ammonio-methacrylate copolymer. The lag time is controlled by the rate of water influx through the polymer membrane. The water dissolves succinic acid and the drug in the core and the acid solution in turn increases permeability of the hydrated polymer film. In addition to succinic acid, acetic acid, glutaric acid, tartaric acid, malic acid, or citric acid can be used. The increased permeability is due improved hydration of film which increases free volume[10].

Low density floating multiparticulate pulsatile systems :

The conventional multiparticulate pulsatile release dosage forms have the longer residence time in the gastrointestinal tract but the variable nature of gastric emptying process result in *in vivo* variability and bioavailability problems. Hence the low density floating multiparticulate pulsatile dosage forms reside only in stomach and not affected by local environment, variability of pH, or gastric emptying rate. These dosage forms are advantageous for drugs either absorbed from the stomach or requiring local delivery in stomach[11].

INTERNAL STIMULI BASED PULSATILE RELEASE:

TEMPERATURE-INDUCED PULSATILE RELEASE

Temperature acts as a stimulus that releases the therapeutic agents from several temperature responsive drug delivery systems for diseases accompanying fever. The temperature induced pulsatile drug delivery systems utilize various polymer properties, including the thermally reversible coil/globule transition of polymer molecules, crystalline melting,swelling change of networks and glass transition.

Thermoresponsive Hydrogel System

The systems consists of hydrogels which shows volume changes in response to changes in temperature. Thermo-sensitive hydrosensitive hydrogels absorbs water and swell at temperatures below the transition temperature whereas they shrink or deswell at temperatures above the transition temperature by expelling water. These Thermally responsive hydrogels and membranes have been widely used for the pulsatile drug delivery

Thermoresponsive Polymeric Micelle System

In this system the gel stores the drug in the micelles and shows a pulsatile release of the drug by switching on-off of external stimuli such as infrared laser beam or temperature[12].

CHEMICAL STIMULI INDUCED PULSATILE SYSTEMS

Glucose Responsive Insulin Release System

The oxidation of glucose to gluconic acid is catalysed by glucose oxidase which lower the pH to approximately 5.8. This enzyme is most widely used in glucose sensing, and makes possible to apply different types of pH sensitive hydro gels for modulated insulin delivery. This change in the pH induces the swelling of polymer which results in the release of Insulin. Insulin by virtue of its action reduces sblood glucose level and thereby gluconic acid level is decreased and system turns to the deswelling mode thereby decreasing the insulin release[13].

pH Sensitive Drug Delivery System

pH-sensitive polymers are polyelectrolytes which consists of the weak acidic or basic groups in their structure that either accept or release protons in response to changes in pH. The pH dependent polymers include cellulose acetate phthalate, polyacrylates, sodium carboxy methyl cellulose[14].

Inflammation Induced Pulsatile Release

Physical or chemical stress such as injury, broken bones, etc., induces the inflammation reaction because of which hydroxylradicals ('OH) are produced from these inflammation-responsive cells. Yui *et al*. fabricated a drug delivery systems with the polymers which responded to the hydroxyl radicals and degraded in a limited manner. Yui and coworkers used hyaluronic acid (HA) in the body which is mainly degraded either by hydroxyl radicals or a specific enzyme hyaluronidase. However the degradation of hyaluronic acid is more dominant and rapid by the hydroxyl radicals than the hyaluronidase when HA is injected at inflammatory sites. Thus, they fabricated the HA crosslinked with ethylene glycol diglycidylether or polyglycerol polyglycidylether. The mechanism involved is the surface erosion type of degradation. Inflammatory diseases such as rheumatoid arthritis can be treated using this type of system[15].

Enzymatically-Activated Liposomes

The system consists of the microcapsules of alginate hydrogels incorporated with the drug loaded liposomes. Liposomes were coated with Phospholipase A2 to achieve a pulsatile release of drug molecules. Phospholipase A2 accumulates at the water/liposome interfaces and removes an acyl group from the phospholipids in the liposome. Destabilized liposomes release the drug molecules, thus the release of the drug is regulated by the rate determining microcapsule membrane[16].

EXTERNALLY REGULATED PULSATILE RELEASE

This system requires externally generated environmental changes to initiate drug delivery. These include magnetic fields, ultrasound, electric field, light.

Magnetic Induces Release

The system consists of the magnetic beads which consists of the drug, magnetic carriers, and materials like magnetite, iron, nickel, cobalt e.t.c., When the magnetic field is applied the magnetic carriers receive the magnetic response from the incorporated materials like magnetite, iron, nickel, cobalt e.t.c., Tingyu Liu, et al. first studied the magnetic sensitive behaviour of ferrogels for the controlled release of drugs. The magnetic hydro gels are fabricated by cross linking of gelatine hydrogels with Fe3o4 nanoparticles with genipin as cross linking agent.

When the external magnetic field is applied the drug released and accumulates around the ferrogels. It disperses immediately when the magnetic field is removed. The drug release from the magnetic hydrogel depends on the particle size of the Fe3O4. Furthermore, rapid slow drug release can be tuneable while the magnetic field was switched from “off” to “on” mode[17].

Ultrasound Induces Release

Ultrasound is mostly used as permeation enhancer for drugs through biological membranes like skin, mucous membrane, intestinal wall and blood vessels. Miyazaki et al. studied ultrasound induced drug release on 5 Flouro uracil which showed a 27 fold release of the drug from an ethylene and vinyl acetate. When the ultrasound is applied the degradation of the polymer occurs and the drug is released from the matrix. As the exposure of the ultrasound increases the drug release increases due to increased degradation of the polymer. Thus the Pulsatile drug release is achieved by the on off application of the ultrasound.

Electric Field Induces Release

Electrically responsive delivery systems are prepared by polyelectrolyte (polymers which contain relatively high concentration of ionisable groups along the backbone chain) and are thus, pH-responsive as well as electro-responsive. When the electric field is introduced by the electrodes parallel to the hydrogels, the hydrogel bend depending on the shape of the gel. The deswelling of the hydrogel occurs when the electrodes are placed perpendicular to the hydrogels[18].

Light Induces Release

Light-sensitive hydrogels have been used in developing display units, optical switches, and ophthalmic drug delivery systems. The interaction between light and material is used to modulate drug delivery. Hydrogel absorb the light and convert it to heat, raising the temperature of composite hydrogel above its LCST. This leads to the hydrogel to collapse and result in the pulsed release of drug from the matrix[19].

MARKETED TECHNOLOGIES OF PULSATILE DRUG DELIVERY:

ORBEXA TECHNOLOGY

Developed by Aptalis Pharmaceutical technology. It is a multiparticulate system with high drug loading capacity. It is suitable for the products that need granulation. This technology consists of beads of prepared by the granulation/extrusion and spheronization methods. These beads can be additionally coated with the polymers to retard the release of drugs. It is also used for proteins and enzymes. It has many applications like Pulsatile delivery, sustained delivery, delayed delivery, complex release patterns, gastric protection, site specific delivery, separation of incompatibilities and combination products[20].

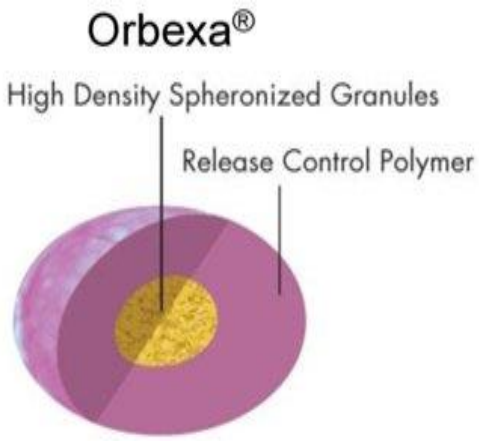

Fig.(1) Orbexa technology.

DIFFUCAPS TECHNOLOGY

This technology is useful for the drugs which show pH dependent solubility and absorption. This ph dependent solubility of drugs is main problem in the formulation of sustained and controlled release formulations. This technology consists of the multiparticulate beads and the beads are multilayered with drug, excepients, release controlling polymers. The beads consists of the layer of organic acid and alkaline buffer to control the solubility of drug by creating the optimal ph environment. The beads are <1.5mm and are filled into capsules or compressed into orally disintegrating tablets[21].

PULSINCAP TECHNOLOGY

Pulsincap was developed by R.R.Scherer International Corporation, Michigan, US. This consists of the insoluble capsule with a hydrogel plug and soluble cap. The entire unit is coated with enteric polymer. When the capsule is placed in the dissolution medium it swells and after a lag time the plug pushes itself outside the capsule and rapidly releases the drug. Another formulation approach is beads or granules which are four layered structures which consists of the core, drug, swelling agent, insoluble polymer. When the system comes in contact with the gastric fluids, due to the swelling of the layer the polymer gets ruptured and leads to rapid release of the drug[22].

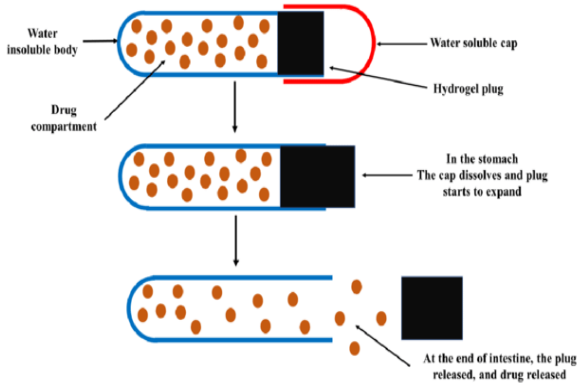

Fig.(2) Pulsincap technology.

CODAS(Chronotherapeutic oral drug absorption system)

Elan Corporation, USA, developed CODAS® technology. It is the multiparticulate system with drug loaded beads which are coated with the non enteric drug release polymers. The polymers are combination of water soluble and water insoluble polymers. When the gastric fluids come in contact with the system the water soluble polymer solublizes and releases drug through the pores formed in the polymer coat. The water insoluble polymer remains insoluble and maintains the controlled release of the drug[23].

OROS TECHNOLOGY

The technology is based on the osmotic system. It consists of the bi or trilayered tablet coated with semi permeable membrane with a drill on the system. One of the layers of the system consisting of the osmotic agent and the other layer consists of the drug. When the system comes in contact with the gastric fluids the osmotic agent swells and pushes the drug through the orifice. This is suitable for drugs having poor solubility[24].

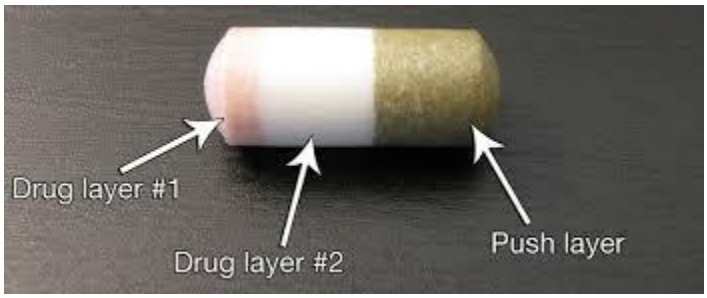

Fig.(3) Oros technology.

GEOCLOCK

The technology is developed by SkyePharma. These are the press coated tablets consists of the active pharmaceutical ingredient and outer layer of hydrophobic wax and brittle material. The outer layer maintains the ph dependent lag time and controlled release of the drug at a predetermined rate[25].

DIFFUTAB TECHNOLOGY

In this technology mixture of hydrophilic and hydrophobic polymers are used to control the drug release. Diffutab technology provides a controlled drug release and site specific drug delivery. The drug released by erosion of the matrix of the tablet or diffusion through techniques. It is useful for sustained release and High dose products[26].

SODAS TECHNOLOGY (SPHEROIDAL ORAL DRUG ABSORPTION SYSTEM)

It is the technology that consists of the multiparticulate beads. The beads consist of the multiple layers of drug, polymers and protective coating. It enables the customized drug release profiles like immediate drug release followed by controlled drug release, Pulsatile release where there is no drug release for several hours.

PRODAS TECHNOLOGY (PROGRAMMED ORAL DRUG ABSORPTION SYSTEM)

It is the multiparticulate system consisting of the minitablets. It enables the controlled release drug delivery. Minitablets of different sizes and release rates are formulated and filled into capsules to attain the customized release[27].

CONTIN TECHNOLOGY

It is developed by Perdue Pharma. The system has the close control over the drug release thus abridge the unwanted side effects. It decreases the frequency of dosing thus increases the patient compliance. In this molecular coordination complexes are formed between the cellulose and non polar solid aliphatic alcohol. It can also achieve by solvating the polymer with volatile polar solvent and react the solvated cellulose with the aliphatic alcohol with a melt method.

EGALET TECHNOLOGY

This technology is developed by the Eaglet Ltd, Denmark. In this technology the drug is sandwiched between the two lag plugs in a shell. When the two plugs are eroded the drug is released from the system after a lag time and it shows a erosion controlled drug release. The shell is made up of the biodegradable polymers and the plugs are made up of the polymers like polyethylene oxide[28].

IPDAS (INTESTINAL PROTECTIVE DRUG SYSTEM) ABSORPTION

This technology consists of the controlled release beads which are compressed to form tablets. It is useful for the gastrointestinal irritant drugs. When the tablet is ingested it disintegrates and releases the beads. The intestinal protection is achieved by the multi particulate system which shows a wide spread of drug throughout the GIT[29].

GEOMATRIX TECHNOLOGY

It is developed by the Skye Pharma Plc, USA. It consists of the multi layered tablets with drug incorporated into the hydrophilic core. The core is coated with the one or two impermeable semi permeable polymer coatings. It has the advantages of incorporation of two drugs and control the release of two drugs simultaneously, easy production, reproducibility, control release of poorly soluble drugs, timed and pulsed release of drugs[30].

CONCLUSION

Pulsatile drug delivery systems are able to deliver drug according to circadian behaviour of disease with the high efficiency and lack of undesirable adverse. The stimuli-responsive feature of these systems is useful for treatment of patients. But major drawbacks arise from the biological variations among individuals. The basic parameters in the design of polymer based pulsatile systems are the biocompatibility and the toxicity of the polymers used. It can be concluded that Pulsatile drug delivery system provide a unique way of delivering drugs possessing chronopharmacological behaviour, extensive first pass metabolism, necessity of night time dosing, or absorption window in GIT. In chronobiology has demonstrated the importance of biological rhythms in drug delivery. Since it seems that timing of drug delivery has significant effect on treatment success. So this can be concluded that pulsatile drug delivery system provides a solution for delivery of drugs for those disease conditions regulated by circadian rhythm.

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