Asian Pac. J. Health Sci., 2018; 5(3):260-270 e-ISSN: 2349-0659, p-ISSN: 2350-0964

Document heading doi: 10.21276/apjhs.2018.5.3.38 Review Article

Pulsatile Drug Delivery System: A Review

Abhimanyu Rai Sharma*, Binu Raina, Prabhjot Singh Bajwa, Anurag Bhargava, Toshiba, Vrinda Goel

Ch. Devi Lal College of Pharmacy, Jagadhri, Yamuna Nagar, Haryana, India

Received: 28-06-2018 / Revised: 01-08-2018 / Accepted: 10-08-2018

ABSTRACT

Pulsatile drug delivery systems have been a major field of research recently. It is the most interesting time-specific and site-specific system. This system is designed for chronopharmacotherapy which is based on circadian rhythm. This means these systems will deliver drug at the time when disease displays it's most morbid and mortal state within a circadian cycle. The use of these systems has been investigated on diseases like asthma, arthritis, ulcers, cardiovascular diseases, hypercholesterolemia, cancer etc. Various capsular, osmotic, single and multiple unit systems that are modulated by soluble or erodible polymer coatings, rupturable membranes are discussed in the article below.

Keywords: Pulsatile, deliver, drug .

Introduction

The oral controlled release drug delivery systems are way much better than the conventional immediate release delivery preparations. With the help of these advanced systems, a drug can be delivered at a controlled and pre- determined rate, therefore, producing their therapeutic effect for a much longer period. Also, for some therapies, a pulsatile drug release pattern is used, in which the drug is released into the body after a well- defined lag time. [1]Pulsatile Drug Delivery System (PDDS) is a time- specific and site-specific drug delivery system, thereby it provides special and temporal delivery and increase patient compliance also. This system can be of great use for the drugs which do not require a constant drug release i.e. do not desire a Zero- order release. PDDS can be defined as the rapid and transient release of certain number of molecules within a short–time immediately after a pre–determined off-release period, i.e. lag time. Lag time is defined as the time between the placement of dosage form into an aqueous environment and the time at which the active ingredient begins to get released from the dosage from. [2]

**Correspondence*
Abhimanyu Rai Sharma
Ch. Devi Lal College of Pharmacy, Jagadhri, Yamuna Nagar, Haryana, India
E-Mail: abhimanyuraisharma@gmail.com

'Chrono pharmaceutics' is a word made after compiling two words, Chronobiology and Pharmaceutics. Chronobiology is the study of biological rhythms and their mechanisms. There are 3 types of mechanical rhythms in our body: -

- **Circadian:** This word comes from Latin word 'circa' means about and 'dies' means day.
- **Ultradian:** Oscillations of shorter duration are termed as ultradian (more than 1 cycle 24 hrs) [5]
- **Infradian:** Oscillations that are longer than 24 hrs (less than one cycle per day) [3]

  It is well- documented that majority of the body functions exhibit circadian rhythms e.g. heart rate, stroke volume, blood pressure, blood flow, body temperature, gastric pH etc. Moreover, in a number of organs their functions vary with the time of the day. [4]

Diseases requiring Pulsatile Drug Delivery

Many of our body functions like metabolism, sleep patterns, behaviour, physiology and hormone production are regulated by circadian rhythm. Capillary resistance and vascular reactivity are higher in the morning and decrease in the day later on. Circadian changes are observed in normal lung functioning, which is very low in early morning hours. Also, Blood pressure is found to be high in the morning and low during night. Rheumatoid arthritis patients suffer more pain in the morning period while osteo- arthritis patients feel more pain in the night time. In all such

diseases, pulsatile drug delivery can be immensely beneficial. [6-7]

Table 1: shows some of the diseases [8]

Disease	Chronological behaviour	Drugs used
Peptic Ulcer	Acid recreation is high in after - noon and at night	H_2 blockers
Asthma	Precipitation of attacks during night or at early morning hours	B^2 agonist, Antihistaminics
Cardiovascular diseases	BP is at its lowest during the sleep cycle and arises steeply during early morning awakening period	Nitro-glycerine, calcium channel blocker, ACE inhibitors etc.
Arthritis	Pain in the morning and more pain at night.	Glucocorticoids.
Diabetes Mellitus	Increase in the blood sugar level after meal	Sulphonyl urea, Insulin.
Attention deficit syndrome	Increase in DOPA level in afternoon.	Methylphenidate
Hypercholesterolemia	Cholesterol synthesis is generally high during night than day time	HMC CoA reductase inhibitors

The shift from conventional sustained release to modern pulsatile drug delivery can be credited to the following reasons

First Pass Metabolism

A few drugs, like beta blockers and salicylic amide, undergo extensive first pass metabolism and require fast drug input to saturate metabolizing enzymes in order to minimize pre-systemic metabolism. Thus, a constant / sustained oral delivery method would result in reduced oral bio- availability.

Biological tolerance: Continuous release drug plasma profiles are often accompanied by a decline in the pharmacotherapeutic effect of the drug, e.g. biological tolerance of transdermal nitro-glycerine.

Special chrono pharmacologicalneeds: Circadian rhythms in certain physiological functions are now well – known and well established. It has been recognized that a lot of symptoms and onset of disease occur at specific time periods of 24-hour day, e.g. asthma and angina pectoris attack we most frequent in morning hours.

Local therapeutic needs: For the treatment of local disorders such as inflammatory bowel disease, there is a need of delivery of compounds at the site of inflammation with no loss due to absorption in small intestine to minimize the side effects.

Gastric irritation or drug instability in gastric fluid: For the compounds with gastric irritation or chemical instability in gastric fluid, the use of sustained release preparation may increase gastric irritation and chemical instability in gastric fluid. [8]

Drug absorption differences in various gastro – intestinal segments

Generally, the drug absorption is moderately slow in the stomach, rapid in the small intestine and sharply declining in the large intestine. So, the drugs targeted to the colon region could not be properly effective due to pre–absorption in earlier gastro- intestinal tract. [8-9]

Methodologies for PDDS

Methodologies for PDDS can be briefly classified into 4 classes,

Time controlled Pulsatile Release
Single Unit System
Multi Particulate System
Stimuli – induced
Thermo – responsive pulsatile release
Chemical stimuli induced Pulsatile systems
External stimuli pulsatile release
Pulsatile release systems for vaccines and hormone products [10]

Time controlled Pulsatile Release System

The time controlled systems can be classified as single unit (e.g. tablets and capsules) or multiple unit systems.

Single unit Systems

Capsular Systems

A variety of single – unit PDDS have been developed. A general layout of such systems consists of an insoluble capsule body consisting of a drug and a plug. This plug is removed after a pre- determined lag time due to swelling, erosion or dissolution.

Pulsincap system is a good example of such a system which is made up of such a system that is made up of a water – insoluble body filled with drug formulation. [11] The body has a closed and an open- end closed with a swellable hydrogel plug. This plug, when comes in contact of the dissolution medium or gastro – intestinal fluids, gets swollen up, and pushes itself out of the capsule after a time lag, which is followed by a spontaneous release of the drug. The time lag can be

controlled by the manipulation of the dimensions and position of the plug. Inclusion of effervescent agents or disintegrants ensures a spontaneous release is case of water insoluble drugs. The plug material consists of insoluble but permeable and swellable polymers [12-13] (e.g. polymethacrylates), erodible compressed polymers (Polyvinyl alcohol, polyethylene oxide), congealed melted polymers (saturated polyglycolated glycerides), controlled erodible polymer .(pectin). These formations are well tolerated in animals and healthy volunteers, and there are no reports of gastro – intestinal irritation. The problem of gastric residence time has been overcome by enteric coating the system to allow its dissolution only in the higher pH region of small intestine.

Port Systems

This system consists of gelatine capsule coated with a semi – permeable membrane (e.g. cellulose acetate) along with an insoluble plug (e.g. lipidic). It also contains an osmotically active agent along with the drug formulation [14]. In presence of an aqueous medium, the water diffuses across the semi- permeable membrane, leading to increased inner pressure that ejects the plug after predetermined time lag. The lag time can be controlled by the thickness of the semi permeable membrane. This system shows a good correlation b/w lag time of in- vitro and in- vivo experiments in human beings. [15].An osmotically driven capsular system was developed to deliver the drug in liquid form. In this system, the liquid drug is absorbed into highly porous particles. These particles release the drug through an orifice of semi – permeable capsule supported by an expanding osmotic layer after the dissolution of the barrier layer. [16] The wall of the capsule is made up of an elastic material and also possesses an orifice. Due to osmosis, there is an increase in the pressure inside the capsule, resulting in stretching of the wall. As the orifice in very minute, there is no flow of drug when the elastic wall relaxes. But as the wall stretches, the orifice also expands sufficiently enough for the release of the drug at a required rate. Styrene –butadiene is one of the suggested elastomers. [17-18]

Delivery by a series of stops

This system is described specifically for the implantable capsules. Here, the capsule consists of a drug along with a water- absorptive osmotic engine which are placed in different compartments separated by a movable partition. The pulsatile delivery is due to a series of stops along the inner wall of the capsule. These stops cause an obstruction in the movement of the partition but later on, due to the rise in osmotic pressure above a threshold level, these obstructions are overcome. The number and frequency of the pulses can be managed by changing number of stops and longitudinal placements in the capsule. Pulse intensity is controlled by the configuration of the partition. Porcine somatotropin was delivered by this system. [19]

Delivery by solubility modulation

A solubility modulator is present for pulsed delivery of a variety of drugs in these systems. The system was especially developed for the delivery of salbutamol sulphate [20]. The compositions consist of a drug (salbutamol sulphate) along with a modulating agent (sodium chloride). The amount of NaCl was less than that required to maintain saturation in a fluid entering the osmotic device. Pulsed delivery depends on the drug solubility. Salbutamol has solubility of 275mg/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 a drug is a function of the modulator's concentration, while the modulator's solubility is largely independent of drug concentration. The modulating agent can be a solid organic acid, inorganic acid or organic salt.

Delivery by reservoir systems with erodible or soluble barrier coatings

PDDS are mostly reservoir devices which are coated with a barrier layer. After a specific lag period, barrier erodes, or dissolves and subsequent and rapid release of drug takes place. The thickness of the coating layer is a factor on which the time lag depends. [21]

The Time Clock System

Consists of a solid dosage form coated with lipid barrier which contain carnauba wax and Bees wax along with surfactants, like, poly oxyethylene sorbitan monooleate. [22] [23] In an aqueous environment, this coat erodes or emulsifies with time proportional to the thickness of the film and the core dispersion takes place. There is no need of any special equipment and the manufacture is easy. However, a premature drug release is often when the penetrating water dissolves the drug.

The Chronotropic System

Consists of a drug containing core coated by hydrophilic swellable hydro propyl methyl cellulose (HPMC), which is mainly responsible for a lag phase in the drug release. The thickness and the viscosity grades of the HPMC used in coating control the time lag. Both tablet and capsule formulations are favoured by this system. [24-25]

Multi – particulate Systems

Multi particulate drug delivery systems are chiefly oral dosage forms consisting of a number of small discrete

units, which contain the active substance as independent sub – units.

Advantages over single – unit systems

They have small size and there is no risk of dose dumping.

There is less inter and intra subject variability in gastro–intestinal transit time.

There are less adverse effects and also improved tolerability.There is flexibility in design and stability also

Disadvantages

Lack of manufacturing reproducibility

High production cost

Multiple formulation steps

Need of advanced technologies. [10]

Different types of multi – particulates systems are described below

Pulsatile system based on rupturable coating

These are multiparticulate systems in which the drug is coated on non- partial sugar seeds followed by a swellable layer and an insoluble top layer coating (Ueda et at 1994). The swelling agents used include super disintegrants like sodium carboxymethyl cellulose, sodium starch glycollate and polymers like polyvinyl acetate, polyacrylic acid, polyethylene glycol etc. Effervescent system comprising a mixture of tartaric acid, citric acid and sodium bicarbonate may also be used alternatively. Upon entrance or ingress of water, the expansion of swellable layer takes place leading to rupture of film with the subsequent rapid drug release. The environmental factors like pH and drug solubility do not affect the release of drug at all. Variation in coating thickness or addition of high amounts of lipophilic plasticizer in the outermost layer can lead to variation in the lag time. With increase in concentration of osmotic agent, a rapid release after the lag phase can be achieved. [26] [27]

Time controlled expulsion system

This system is based on a combination of osmotic and swelling factors. The core consists of the drug, a low bulk density solid and/or liquid lipid material (e.g. mineral oil) and a disintegrant also. The core further contains a coating of cellulose acetate. When immersed in an aqueous medium, the water penetrates the core and displaces the lipid material [28]. Subsequently, an increase in internal pressure takes place resulting in rupturing of the coating material. This system is also known as Osmotic based rupturable coating system. Another system is based on a capsule or tablet composed of a large no. of pellets with different release pattern. [29] The core consists of the therapeutic drug and a water soluble osmotic agent in each pellet. The core is enclosed by water – permeable, water insoluble polymer film. The polymer film is incorporated with a hydrophobic, water insoluble agent that alters the permeability (e.g. wax, fatty acid or a salt of fatty acid). The film coating of each population differs from another pellet coating due to water influx and drug efflux. The rate of drug diffusion is regulated by the swelling of pellets due to the dissolution of osmotic agent. A single dosage form provides a series of pulses as each pellet population releases its drug content. This system was used for the delivery of anti- hypertensive drug diltiazem.Also, some osmotically active agents are used that do not undergo swelling. These pellet cores consist of drug along with sodium chloride coated with semi-permeable cellulose acetate polymer. The coat is selectively permeable to water and is impermeable to the drug. The presence of sodium hydroxide produces fast release of drug while its absence gives sustained release after the lag time. [30]

Pulsatile Delivery by change in Membrane Permeability

The presence of different counter–ions in the medium can influence the permeability and water uptake of acrylic polymers with quaternary ammonium groups [31]. Several delivery systems based on this ion exchange have been developed. Eudragit is a polymer of choice for this purpose [32]. It contains positively polarized quaternary ammonium group in the polymer side chain, that are always accompanied by negative hydrochloride counter ions. As the ammonium group is hydrophilic, it facilitates the interaction of polymer with water and thereby changes its permeability and allows the water to permeate the active core in a controlled manner. This property is essential to achieve precisely defined lag time. Theophylline, was used as model drug with sodium acetate used to prepare the cores. These pellets were coated using Eudragit (10% to 40% weight gain) in 4 different layer thicknesses. A correlation b/w film thickness and lag time was observed. The permeability of the eudragit film was affected dramatically even with a small amount of sodium acetate in the pellet core. After the lag time, the interaction between acetate and polymer increases the permeability of the coating such that the entire dose is liberated within a few minutes. [31] The lag increases with increasing thickness of the coat, but the release of drug was not affected by this thickness and depended on the amount of salt present in the system.

Sigmoidal Release System

This system comprises of pellet core containing drug and succinic acid coated with ammonia – methacrylate copolymer. [33] The permeability of the film is enhanced by the drug inside and the acid solution. The water in the medium dissolves Succinic acid. In place

of succinic acid, acetic acid, glutaric acid, tartaric acid, malic acid and citric acid is also used. This system was used to design an acid containing core.(Narisowa et at. 1994,1996) [34] [35] [36]

Low Density floating multi – particulate pulsatile systems

All the systems mentioned above have longer residence time in gastro – intestinal tract and may result in 'in vivo' variability and bio- availability problems. On the other hand, low density floating multi particulate systems reside only in stomach and are independent of variability of pH, local environment or gastric emptying rate. These are specifically advantageous for drugs either absorbed by stomach or those requiring local delivery in stomach. [37]

Stimuli – induced pulsatile systems

In these systems, stimulation by any biological factor like temperature or any other chemical stimuli leads to release of the drug [38]. Further classification is as follows

Thermo – responsive Pulsatile Release

Thermo – responsive hydrogel systems have been developed for pulsatile release. In these systems, the polymer swells or deswells in response to temperature which modulate drug release in swollen state (Survase et at 2007) [39]

Chemical stimuli induced Pulsatile system

Glucose – responsive Insulin release devices

In the case of Diabetes mellitus, a rhythmic increase in the levels of glucose is noticed in the body, requiring an injection of insulin at proper time. Several systems which are able to respond to changes in glucose concentration have been developed. One such system includes pH sensitive Hydrogel containing glucose oxidase immobilized in the hydrogel. Upon the increment of glucose concentration in the blood, Glucose is converted into Gluconic Acid by Glucose oxidase which changes the pH of the system. This change in the pH induces swelling of polymer which results in insulin release. Insulin by its action, reduces blood glucose level and consequently gluconic acid level is also decreased and the system turns to deswelling mode thereby decreasing the insulin release. Examples of pH sensitive polymers include N, N – dimethyl aminoethyl methacrylate, chitosan, polyol etc. [40-42]

Inflammation induced pulsatile release

Inflammation is a natural phenomenon that occurs on receiving any physical or chemical stress such as injury, fracture etc. at the injured site. These inflammation responsive cells produce hydroxyl radicals. It is possible to treat patients with inflammatory diseases like rheumatoid arthritis, using anti – inflammatory drug incorporated HA gels or Hyaluronic Acid gels as new implantable drug delivery system. [42-43]

Drug release form intelligent gels responding to antibody concentration

Numerous kinds of bioactive compounds 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. The antigen – antibody complex formation was given special attention as cross – linking units in the gel, since such interaction is very specific. Utilizing the difference between polymerized antibodies and naturally derived antibodies' association constants towards specific antigens, reversible gel swelling/ deswelling and drug permeation changes occurs. [39] [42]

pH sensitive Drug Delivery System

This system comprises of 2 components – fast release type and pulsed release type. The pulsed release type releases drug in response to change in pH. Its main advantage is the fact that there exists different pH environment at different parts of the GIT. Drug release at specific location can be obtained by selecting pH dependent polymers like acetate phthalate, poly acrylates and sodium carboxy methyl cellulose. The polymers are used as enteric coating materials so as to provide release of drug in the small intestine. [39]

External Stimuli Pulsatile release

These systems are not self – regulating, but instead require externally generated environmental changes to initiate drug delivery. These can include magnetic fields, ultrasound, temperature, light etc.

Magnetic Field

Use of an oscillating magnetic field to modulate the rates of drug delivery from a polymer matrix was one of the first methodologies investigated to achieve an externally controlled drug delivery system. [44]

Magnetic steel beads were embedded in an ethylene and vinyl acetate (EVAC) copolymer matrix that was loaded with bovine serum albumin as a model drug. [45]

During exposure to magnetic field, the beads start oscillating within the matrix, therefore creating compressive and tensile forces. These forces act as a pump to push an increased amount of the drug molecule out of the matrix. The co-polymers having higher Young's modulus were more resistant to induced motion of steel beads, thereby, magnetic field has less effect on rate of drug release from these materials. [46]

Also, different Formulations were developed for in-vitro magnetically triggered delivery of insulin based on alginate spheres. [47]

A treatment method that involves the administration of a magnetic material composition, which contains single-domain magnetic particles attached to a target-specific ligand, to a patient and the application of an alternating magnetic field to inductively heat the magnetic material composition, which cause the triggered release of therapeutic agents at the target tumour or cancer cells, also exists. [48]

Ultrasound

Ultrasound is used for improving drug permeability across biological barriers such as skin, lungs, intestinal wall and blood vessels. Many reports describe the effect of ultrasound on controlled drug delivery. [49-55] Kost et.at described an ultrasound – enhanced polymer degradation system.

As degradation of biodegradable matrix was enhanced by ultrasonic exposure, the rate of drug release also increased. Therefore, pulsed drug delivery was achieved by the on- off application of ultrasound. [56] Supersaxo et. at also reported macromolecular drug release from biodegradable poly microspheres. A sustained release can be maintained up to a several months. Authors speculated that ultrasonic exposure results in the enhancement of water permeability within microspheres of the polymer matrix, inducing drug dissolution into the releasing media. [57] There was an increase up to 27 times in the release of 5 Fluorouracil from an ethylene and vinyl acetate matrix using Ultrasound. an increase in the strength of ultrasound resulted in a proportional increase of 5 fluorouracil. [58]Increase in the rate of p-nitroaniline from a polyanhydide matrix during ultrasonic irradiation is reported [59]. It was noted that there was an increase in drug delivery was greater than the increase in matrix erosion when the ultrasound triggering was active. therefore, it was hypothesised that acoustic cavitation by ultrasonic irradiation was responsible for the modulated delivery of p-nitroaniline. [50]

Temperature

Temperature is most widely utilized stimulus for a variety of pulsatile drug delivery systems. Its use has been justified by the fact that the temperature of human body often deviates from physiological temp i.e. 37^{o}c. Bae. Y.H. et. al. developed Indomethacin pulsatile drug delivery system in temperature range between 20-30 degree Celsius by using reversible swelling properties of co polymer of N-isopropylacrylamide and butyryl acrylamide. [60] This deviation can be used as a stimulus that activates the release of the therapeutic agents from various temperature – responsive drug delivery systems for disease accompanying fever. Thermal stimuli – regulated pulsed drug release is established through the design of drug delivery devices such as hydrogels and micelles. [61]

Thermo-responsive hydrogel systems comprise of hydrogels that undergo reversible volume changes in response to changes in the temperature. These thermally-responsive hydrogels and membranes have been evaluated extensively for the pulsatile drug delivery of the drugs.[62].For example, thermally-responsive poly(N-isopropyl acryl amide)(PIPAAm), which show swelling at temperatures below 32 degrees and shrinking above this temperature. Drug release from the PIPAAm hydrogels at temperature below 32degrees was governed by Diffusion but above this temperature the drug release was completely stopped because of the 'skin layer ' formation on the gel surface (on-off drug release regulation).[63-66] PIPAAm hydrogels showed rapid deswelling kinetics without any formation of skin layer on surface .This is possibly due to rapid dehydration of graft chains formed by hydrophobic aggregation on the three-dimensional cross-linked chains. [67-68] Also a similar rapid deswelling phase was achieved by incorporation of poly(ethylene glycol) graft chains in PIPAAm cross linked hydrogels. [69]

Yuk et al. designed temperature -sensitive drug delivery systems using a mixture of poly (ethylene oxide)-poly (propylene oxide)-poly (ethylene oxide) triblock copolymer (F-68) and poly vinyl alcohol(PVA) [70]. The ratio of F-68/PVA could be changed to alter the swelling transition of polymer complex gel. The pulsatile release of acetaminophen in response to pulsatile change in temperature between 35 and 40ºC. [71]US Patents 6733788 and 200200151712 describe a medical device consisting thermo-sensitive cellulose gel structure, through which the bioactive solute compound is delivered to a target location in the body. [72-73]

Thermo – responsive polymeric micelle systems constitute polymeric micelles whose properties and biological interests make them most noteworthy candidate as drug carrier for the treatment of cancer. [74] The polymeric micelle consists of amphiphilic block copolymers exhibiting a hydrophobic core with a hydrophilic corona. Due to such properties, these polymer micelles exhibit stealth characteristics and are not detected by the body defence system. Thus, passive targeting could be achieved through enhanced permeation retention (EPR) effect of tumoursites. [75] Okano and co-workers made the use of an end functionalized PIPAAm to prepare block copolymers. Hydrophobic Polymers, likepoly (butyl methacrylate)

(PBMA), Polystyrene (PSt), [76-77], poly (lactic acid) (PLA) [78-79] have been used.

Electric Field

An electric field works as an external stimulus with several advantages like availability of equipment's, which allows precise control with regards to the magnitude of current, duration of electric pulses, interval between pulses etc.

The mechanism of drug release chiefly includes ejection of drug from the gel as the fluid phase synereses out, drug diffusion along a concentration gradient, the electrophoresis of charged drug towards an oppositely charged electrodes and liberation of the entrapped drug as the gel complex erodes. [80]

Pulsatile release systems for vaccine and hormone products

Vaccines are traditionally administered as an initial shot of an antigen followed by repeated booster shots to produce protective immunity [81]. The frequency of the booster shots and therefore the exact immunization schedule depends on the antigen. Also, co-administration of vaccine adjuvant is given for the enhancement of immune response to achieve protective immunity. [82] PDDS offers the possibility of single – shot vaccines if initial booster release of the antigen can be achieved from one system in which timing of booster release is controlled.

Recent techniques of Oral Time Controlled Pulsatile Technology

The current focus of the pharmaceutical companieshas been on development and commercialization of PDDS that fulfils unmet medical needs in treatment of various diseases. Here are few recently developed technologies. [10]

CODAS Technology

Chronotherapeutic Oral Drug Absorption System (COADS) is a multi-particulate system, which is dosed at bed time that delays drug release 4-5 hrs. The delay is due to the presence of non- enteric coating of the drug loaded beads. The technique has been used in formulation of Verapamil extended release capsules Verelan. [38]

CEFORM Technology

This technique helps in the development of microspheres of uniform size and shape. It is based on "melt spinning" in which biodegradable polymer or bioactive agent's combination is subjected to combination of temperature, thermal gradients, flow, flow rates during processing. These microspheres can be used in tablet, capsule, suspension, sachet form. Coating can also be done to get controlled release. [38]

PULSYS

This technology was used to develop chromotherapeutic system for amoxicillin. As the antibiotics are more effective against fast growing bacteria, this system was designed. On the administration of immediate release system, bacteria respond to it by going into dormant stage, while, in pulsatile drug delivery system, pulses are released at regular intervals, so bacteria do not get to go into the dormant stage effectiveness of this technique has been proved. [83]

GEOCLOCK Technology

Geoclock tablets have an active drug inside an outer tablet layer consisting of a mixture of hydrophobic wax and brittle material in order to obtain a pH – independent lag time prior to core drug delivery at a pre- determined release rate. This dry coating approach is designed to allow the timed release of both slow release and fast release active cores by releasing inner core tablet first after which the surrounding outer shell gradually disintegrates. This technology has been used to develop Lodotra, a rheumatoid arthritis drug, which delivers the active pharmaceutical ingredient at most suitable time of day to treat the disease condition. [84]

Conclusion

By now, oral delivery of drugs is most pregnable route of drug delivery due to the ease of administration, patient compliance, and flexibility in its formulations. Generally, a sustained and controlled release product provide a desired therapeutic effect but fall short of diseases following circadian rhythms.

PDDS can very efficiently tackle the disorders following a circadian rhythm as it is modulated according to body's circadian rhythm giving rise to drug release at specified time lag.

However, for the last two decades, a significant progress has been made towards achieving PDDS that is capable of treating diseases with non- constant dosing therapies. Various pulsatile technologies are on their ways and some are currently in the market.

References

1. Efentakis M, Koligliati S, Vlachou M. Design and evaluation of a dry coated drug delivery system with an impermeable cup, swellable top layer and pulsatile release. International journal of Pharmaceutics. 2006 ;311(1-2):147-56.
2. Rubinstein A, Tirosh B, Baluom M, Nassar T, David A, Radai R, Gliko-Kabir I, Friedman M. The rationale for peptide drug delivery to the

colon and the potential of polymeric carriers as effective tools. Journal of controlled release. 1997;46(1-2):59-73.

3. Youan BB. Chronopharmaceutics: gimmick or clinically relevant approach to drug delivery? Journal of Controlled Release. 2004 ;98(3):337-53.
4. Lemmer B.; Chronopharmacokinetics: implications for drug treatment, J.Pharm. Pharmacol. 51,887-890
5. Smolensky m., D'Alonso G.; Biological rythms and medicines. Am J. Med. 1988; 85:34-46
6. Rasve G., BoradeG., Deshmukh S. and Tagalpallewar A.; "Pulsatile drugdelivery: Current Scenario" International Journal of pharma and bio-sciences;2011;1(3):11
7. Aithal KB, Harish NM, Rathnanand M, Shirwaikar A. Chronotherapeutics and disease management: Treatment in synchrony with body's rhythms-An emerging science. Pharma Times. 2006;38(10):15-8.
8. Kakar Satinder, Singh Ramandeep, Batra Deepa, Nautiyal Ujjwal. Review on recent trends in pulsatile drug delivery systems. Universal journal of pharmacy,2013;2(1):21-41.
9. Burnside B, A., Guo X., Fiske K., CouchR.A., TreacyD.J., Chang R.K., McGuinnes, C.M., Rudnic, E.M.:US20036605300, (2003)
10. Sharma GS, Srikanth MV, Uhumwangho MU, Phani KK, Ramana KM. Recent trends in pulsatile drug delivery systems-A review. International Journal of Drug Delivery. 2010;2(3):21
11. Saeger H, Pulsincap VP. Mac226: Pulsed-Release Dosage Form. Scherer DDS, Ltd. 2004.
12. Krögel I, Bodmeier R. Pulsatile drug release from an insoluble capsule body controlled by an erodible plug. Pharmaceutical research. 1998 ;15(3):474-81.
13. Krögel I, Bodmeier R. Evaluation of an enzyme-containing capsular shaped pulsatile drug delivery system. Pharmaceutical research. 1999 ;16(9):1424-9.
14. Crison JR. Programmable oral release technology, PORT Systems^< (! R)>: A novel dosage form for time and site-specific oral drug delivery. InProc. Intern. Symp. Control. Rel. Bioact. Mater. 1995 ; 22:278-279).
15. Crison JR, Siersma PR, Amidon GL. A novel programmable oral release technology for delivering drugs: human feasibility testing using gamma scintigraphy. InProceed Intern Symp Control Rel Bioact Mater 1996 ;23:51-52
16. Pollock Dove C, Dong L, Wong P. A new system to deliver a delayed bolus of liquid drug formulation. InProceed Intern Symp Control Rel Bioact Mater 2001;28:6033
17. Linkwitz A, Magruder JA, Merrill S, inventors; Alza Corp, assignee. Osmotically driven delivery device with expandable orifice for pulsatile delivery effect. United States patent US 5,318,558. 1994 Jun 7.
18. Linkwitz A, Magruder JA, Merrill S, inventors; Alza Corp, assignee. Osmotically driven delivery device with expandable orifice for pulsatile delivery effect. United States patent US 5,221,278. 1993 Jun 22.
19. Balaban SM, Pike JB, Smith JP, Baile CA, inventors; Alza Corp, assignee. Osmotically driven delivery devices with pulsatile effect. United States patent US 5,209,746. 1993 May 11.
20. Magruder PR, Barclay B, Wong PS, Theeuwes F, inventors; Alza Corp, assignee. Composition comprising salbutamol. United States patent US 4,751,071. 1988 Jun 14.
21. Pozzi F, Furlani P. Orale Feste Pharmazeutische Darreichungsform Mit Programmierter Freisetzung. DE Patent. 1992(4122039).
22. Wilding IR, Davis SS, Pozzi F, Furlani P, Gazzaniga A. Enteric coated timed-release systems for colonic targeting. International journal of pharmaceutics. 1994;111(1):99-102.
23. Gazzaniga A, Iamartino P, Maffione G, Sangalli ME. Oral delayed-release system for colonic specific delivery. International Journal of Pharmaceutics. 1994 ;108(1):77-83.
24. Maroni A, Sangalli M, Cerea M, Busetti C, Giordano F, Gazzaniga A. Low viscosity HPMC coating of soft and hard gelatin capsules for delayed and colonic release: preliminary investigations on process parameters and in vitro release performances. Proceedings of the Controlled Release Society. 1999;26(26):885-6.
25. Ueda Y, Hata T, Yamaguchi H, Ueda S, Kodani M, inventors; Fujisawa Pharmaceutical Co Ltd, assignee. Time-controlled explosion systems and processes for preparing the same. United States patent US 4,871,549. 1989 Oct 3.
26. Ueda Y., Hata T., Yamaguchi H., Kotani M., Ueda S.; Development of a drug release system, Time Controlled Explosion System (TCES). PartI: concept and design. J Drug Targeting 1994; 2:35-44
27. Amidon GL, Leesman GD, inventors; University of Michigan, assignee. Pulsatile drug delivery

system. United States patent US 5,229,131. 1993 Jul 20.

28. Chen CM, inventor; Andrx Pharmaceuticals Inc, assignee. Multiparticulate pulsatile drug delivery system. United States patent US 5,508,040. 1996 Apr 16.

29. Bodmeier R, Guo X, Sarabia RE, Skultety PF. The influence of buffer species and strength on diltiazem HC1 release from beads coated with the aqueous cationic polymer dispersions, Eudragit RS, RL 30D. Pharmaceutical research. 1996 ;13(1):52-6.

30. Schultz P, Kleinebudde P. A new multiparticulate delayed release system.: Part I: dissolution properties and release mechanism. Journal of controlled release. 1997 ;47(2):181-9.

31. Beckert TE, Pogarell K, Hack I, Petereit HU. Pulsed drug release with film coatings of Eudragit & Mac226; RS 30D. InPrecede Int. Symp Control Release Bioact Mater 1999 ;26: 533-4

32. Narisawa S, Nagata M, Danyoshi C, Yoshino H, Murata K, Hirakawa Y, Noda K. An organic acid-induced sigmoidal release system for oral controlled-release preparations. Pharmaceutical research. 1994 ;11(1):111-6.

33. Guo X. Physicochemical and mechanical properties influencing the drug release from coated dosage forms (Doctoral dissertation, University of Texas at Austin).

34. Narisawa S, Nagata M, Ito T, Yoshino H, Hirakawa Y, Noda K. Drug release behavior in gastrointestinal tract of beagle dogs from multiple unit type rate-controlled or time-controlled release preparations coated with insoluble polymer-based film. Journal of controlled release. 1995 ;33(2):253-60.

35. Narisawa S, Nagata M, Hirakawa Y, Kobayashi M, Yoshino H. An organic acid- induced sigmoidal release system for oral controlled- release preparations. Journal of pharmaceutical sciences. 1996;85(2):184-8.

36. Roy P, Shahiwala A. Multiparticulate formulation approach to pulsatile drug delivery: current perspectives. Journal of controlled release. 2009 ;134(2):74-80.

37. Lee DY, Chen CM, Anil K. Triggered Release of Bioactive Compounds, Recent Patents on Endocrine. Metabolic & Immune Drug Disc. 2007; 1:183-90.

38. Singh A, Dubey H, Shukla I, Singh DP. Pulsatile drug delivery system: an approach of medication according to circadian rhythm. J. App. Pharm. Sci. 2012; 2:166-76.

39. Survase S, Kumar N. Pulsatile drug delivery: Current scenario. CRIPS. 2007 ;8(2):27-33.

40. Gutowska A, Bark JS, Kwon IC, Bae YH, Cha Y, Kim SW. Squeezing hydrogels for controlled oral drug delivery. Journal of Controlled Release. 1997 ;48(2-3):141-8.

41. Nobuhiko Y, Teruo O, Yasuhisa S. Inflammation responsive degradation of crosslinked hyaluronic acid gels. Journal of Controlled release. 1992 ;22(2):105-16.

42. Kikuchi A, Okano T. Pulsatile drug release control using hydrogels. Advanced drug delivery reviews. 2002 ;54(1):53-77.

43. Miyata T, Asami N, Uragami T. A reversibly antigen-responsive hydrogel. Nature. 1999 ;399(6738):766

44. Hsieh DS, Langer R, Folkman J. Magnetic modulation of release of macromolecules from polymers. Proceedings of the National Academy of Sciences. 1981;78(3):1863-7.

45. Edelman ER, Kost J, Bobeck H, Langer R. Regulation of drug release from polymer matrices by oscillating magnetic fields. Journal of biomedical materials research. 1985 ;19(1):67-83

46. Kost J, Noecker R, Kunica E, Langer R. Magnetically controlled release systems: effect of polymer composition. Journal of biomedical materials research. 1985 19(8):935-40.

47. Saslawski O, Weingarten C, Benoit JP, Couvreur P. Magnetically responsive microspheres for the pulsed delivery of insulin. Life Sciences. 1988 ;42(16):1521-8.

48. Handy E.S., Ivkov R., Ellis-Busby D., Foreman A., Braunhut S.J., Gwost D.U., Ardman B.; "Thermo therapy via targeted delivery of nanoscale magnetic particles"; US Patent No. US997863,2006

49. Levy D, Kost J, Meshulam Y, Langer R. Effect of ultrasound on transdermal drug delivery to rats and guinea pigs. The Journal of clinical investigation. 1989;83(6):2074-8.

50. Kost J., Ultrasound for controlled delivery of therapeutics; Clin. Mater., 1993,13,15

51. Machluf M, Kost J. Ultrasonically enhanced transdermal drug delivery. Experimental approaches to elucidate the mechanism. Journal of Biomaterials Science, Polymer Edition. 1994 ;5(1-2):147-56

52. Mitragotri S, Blankschtein D, Langer R. Ultrasound-mediated transdermal protein delivery. Science. 1995 ;269(5225):850-3.

53. Mitragotri S, Blankschtein D, Langer R. Transdermal drug delivery using low-frequency sonophoresis. Pharmaceutical research. 1996;13(3):411-20

54. Byl NN. The use of ultrasound as an enhancer for transcutaneous drug delivery: phonophoresis. Physical therapy. 1995;75(6):539-53.

55. Mitragotri S. Synergistic effect of enhancers for transdermal drug delivery. Pharmaceutical research. 2000 ;17(11):1354-9

56. Kost J, Leong K, Langer R. Ultrasound-enhanced polymer degradation and release of incorporated substances. Proceedings of the National Academy of Sciences. 1989;86(20):7663-6.

57. Supersaxo A, Kou JH, Teitelbaum P, Maskiewicz R. Preformed porous microspheres for controlled and pulsed release of macromolecules. Journal of controlled release. 1993;23(2):157-64

58. Miyazaki S, Hou W, Takada M. Controlled drug release by ultrasound irradiation. Chemical and pharmaceutical bulletin. 1985 ;33(1):428-31.

59. Leong K.W., KostJ., Mathiowitz F., Langer R.; Polyanhydrides for controlled release of bioactive agents; Biomaterials ,1986;7:364

60. Satinder Kakar, Ramandeep Singh, Alok Semwal. Drug release characteristics of dosage forms: a review. Journal of Coastal Life Medicine.2014;2(4):332-336

61. Bae YH, Okano T, Kim SW. "On–Off" thermocontrol of solute transport. I. Temperature dependence of swelling of N-isopropylacrylamide networks modified with hydrophobic components in water. Pharmaceutical research. 1991;8(4):531-7.

62. Bae YH, Okano T, Kirn SW. "On–Off "Thermocontrol of Solute Transport. II. Solute Release from Thermosensitive Hydrogels. Pharmaceutical research. 1991;8(5):624-8

63. Dong LC, Hoffman AS. Synthesis and application of thermally reversible heterogels for drug delivery. Journal of controlled release. 1990 ;13(1):21-31.

64. Satinder Kakar,Anurekha Jain, Ramandeep Singh. Magnetic microspheres: a novel targeting delivery system. FABAD. 2017;42(3):191-206

65. Kaneko Y, Sakai K, Kikuchi A, Yoshida R, Sakurai Y, Okano T. Influence of freely mobile grafted chain length on dynamic properties of comb-type grafted poly (N-isopropylacrylamide)hydrogels.Macromolecules. 1995;28(23):7717-23.

66. Kaneko Y, Sakai K, Kikuchi A, Yoshida R, Sakurai Y, Okano T. Influence of freely mobile grafted chain length on dynamic properties of comb-type grafted poly (N-isopropylacrylamide) hydrogels. Macro molecules. 1995;28(23):7717-23

67. Kaneko Y, Sakai K, Kikuchi A, Sakurai Y, Okano T. Fast swelling/deswelling kinetics of comb- type grafted poly (N- isopropylacrylamide) hydrogels. InMacromolecular Symposia 1996 May (Vol. 109, No. 1, pp. 41-53). Basel: Hüthig & Wepf Verlag.

68. Kaneko Y, Nakamura S, Sakai K, Aoyagi T, Kikuchi A, Sakurai Y, Okano T. Rapid deswelling response of poly (N-isopropylacrylamide) hydrogels by the formation of water release channels using poly (ethylene oxide) graft chains. Macromolecules. 1998 ;31(18):6099-105

69. Kim SY, Lee YM. Drug release behavior of electrical responsive poly (vinyl alcohol)/poly (acrylic acid) IPN hydrogels under an electric stimulus. Journal of Applied Polymer Science. 1999 ;74(7):1752-61.

70. Oh KS, Han SK, Choi YW, Lee JH, Lee JY, Yuk SH. Hydrogen-bonded polymer gel and its application as a temperature-sensitive drug delivery system. Biomaterials. 2004 May 1;25(12):2393-8.

71. McBride JF, Gehrke SH, Fisher JP, inventors; Boston Scientific Scimed Inc, assignee. Temperature controlled solute delivery system. United States patent US 6,733,788. 2004 May 11.

72. Mebride J.F., Gehrker S.H., Fisher J.P.; US Patent no. US0015712,200

73. Kataoka K, Harada A, Nagasaki Y. Block copolymer micelles for drug delivery: design, characterization and biological significance. Advanced drug delivery reviews. 2012; 64:37-48.

74. Matsumura Y, Maeda H. A new concept for macromolecular therapeutics in cancer chemotherapy: mechanism of tumoritropic accumulation of proteins and the antitumor agent smancs. Cancer research. 1986 ;46(12 Part 1):6387-92.

75. Chung JE, Yokoyama M, Yamato M, Aoyagi T, Sakurai Y, Okano T. Thermo-responsive drug delivery from polymeric micelles constructed using block copolymers of poly (N-isopropylacrylamide) and poly (butylmethacrylate). Journal of Controlled Release. 1999;62(1-2):115-27.

76. Chung JE, Yokoyama M, Okano T. Inner core segment design for drug delivery control of

thermo-responsive polymeric micelles. Journal of Controlled Release. 2000;65(1-2):93-103.

77. Kohori F, Sakai K, Aoyagi T, Yokoyama M, Sakurai Y, Okano T. Preparation and characterization of thermally responsive block copolymer micelles comprising poly (N-isopropylacrylamide-b-DL-lactide). Journal of controlled release. 1998;55(1):87-98.

78. Kohori F., Sakai K., Aoyagi T., Yokoyama M., Sakurai Y., OkanoT.; Colloids Surfaces B: Biointerfaces, 1999,16,195

79. MurdanS.; Electro responsive drug delivery from hydrogels; J. Control Release ,2003,92.1

80. Ada G. Strategies for exploiting the immune system in the design of vaccines. Molecular immunology. 1991 ;28(3):225-30.

81. Gupta RK, Relyveld EH, Lindblad EB, Bizzini B, Ben-Efraim S, Gupta CK. Adjuvants—a balance between toxicity and adjuvanticity. Vaccine. 1993 Jan 1;11(3):293-306.

82. Parmar RD, Parikh RK, Vidyasagar G, Patel DV, Patel CJ, Patel BD. Pulsatile drug delivery systems: an overview. Int J Pharm Sci Nanotechnol. 2009 ; 2:605-14.

83. Eshant Duggal, Pankaj Kashyap, Ramandeep Singh, Satinder Kakar. Fast track approaches for drug approval across the globe. Asian Pacific Journal of Health Sciences, 2014; 1(1): 2-12

Conflict of Interest: None
Source of Support: Nil