JPRHC

Review Article

PULSATILE DRUG DELIVERY SYSTEM: AN "USER-FRIENDLY" DOSAGE FORM

JIGAR D. PATEL *, KRITIKA ANEJA, SHIVPRASAD H. MAJUMDAR

For Author Affiliations, See end of the text

ABSTRACT

In the body under physiological conditions, many vital functions are regulated by transient release of bioactive substances at a specific time and site. Thus, to mimic the function of living systems and in view of emerging chronotherapeutic approaches, which lead to development of pulsatile system that release a therapeutic agent at a rhythm that ideally matches the biological requirement of a given disease therapy. Diseases where a constant drug levels are not preferred, but needs a pulse of therapeutic concentration in a periodic manner and diseases with established oscillatory rhythm in their pathogenesis includes asthma, arthritis, duodenal ulcer, cancer, cardiovascular diseases acts as a push for the development of "Pulsatile Drug Delivery Systems ". In these systems, there is rapid and transient release of a certain amount of drug molecules within a short time-period immediately after a predetermined off release period. Various techniques are available for the pulsatile delivery like pH dependent systems, time dependent systems, etc. Pulsatile drug delivery system providing special and temporal delivery and increasing patient compliance. Pulsatile drug delivery system is defined as the rapid and transient release of certain amount of molecules within a short time period immediately after predetermined off-release periods i.e. lag time. Advantages of the pulsatile drug delivery system are reduced dose frequency; reduce side effects, drug targeting to specific site like colon and many more. Now in market varies technologies of pulsatile drug delivery system like OROS, CODAS etc. are launched by pharmaceutical companies.

Keywords:- Chronotherapeutic , Preplanned System , Externally regulated system , Pulsatile drug delivery system

Review Article

INTRODUCTION

Nowadays, the emphasis of pharmaceutical galenic research is turned towards the development of more efficacious drug delivery systems with already existing molecule rather going for new drug discovery becauseof the inherent hurdles posed in drug discovery and development process[1].

Pulsatile system is amongst one of them and gaining a lot of interest as it is increasing patient compliance by means of providing time- and site-specific drugdelivery system, thus providing special and temporal delivery. A pharmaceutical dosage form such as a capsule capable of delivering therapeutic agents into the body in a time-controlled or position-controlled pulsatile release fashion, is composed of a multitude of multicoated particulates (beads, pellets,granules, etc.) made of one or more populations of beads. On which cases or circumstance pulsatile drug delivery is used they are listed below.

1) Chronopharmacotherapy of diseases which shows circadian rhythms in their pathophysiology.
2) Avoiding the first pass metabolism e.g. protein and peptides[2]
3) For which the tolerance is rapidly exists,
4) For targetting specific site in intestine e.g. colon,
5) For time programmed administration of hormone and drugs,
6) For drugs having the short half life

Drugs which exhibit tolerance should not be delivered at a constant rate, since the drug effect decreases with time at constant drug level. In addition drug toxicity increases with time when drug levels are held constant. In such cases it is preferable to opt for dosage form which will provide desired concentration of drug at particular time point only[3]. Now, concept of chronopharmaceutics has emerged, wherein, research is devoted to the design and evaluation of drug delivery systems that release a therapeutic agent at a rhythm that ideally matches the biological requirement of a given disease therapy. "Chronopharmaceutics" consist of two words chronobiology and pharmaceutics. Chronobiology is the study of biological rhythms and their mechanisms.

There are three types of mechanical rhythms in our body. They are:

i. Circadian

ii. Ultradian

iii. Infradian

Circadian

This word comes from Latin word "circa" means about and "dies" means day

Ultrdian

Oscillation of shorter duration are termed as ultradian (more than one cycle per 24 h)

Infradian

Oscillations that are longer than 24 h (less than one cycle per day)Diseases where a constant drug levels are not preferred, but needs a pulse of therapeutic concentration in a periodic manner acts as a push for the development of "Pulsatile Drug Delivery Systems"[4].

The diseases that are targeted for chronopharmaceutics are those which establish oscillatory rhythm in their pathogeneisis. These diseases include asthma, arthritis, duodenal ulcer, cancer, cardiovascular diseases (e.g., hypertension and acute myocardial infarction, hypercholesterolemia, and ulcer).

Review Article

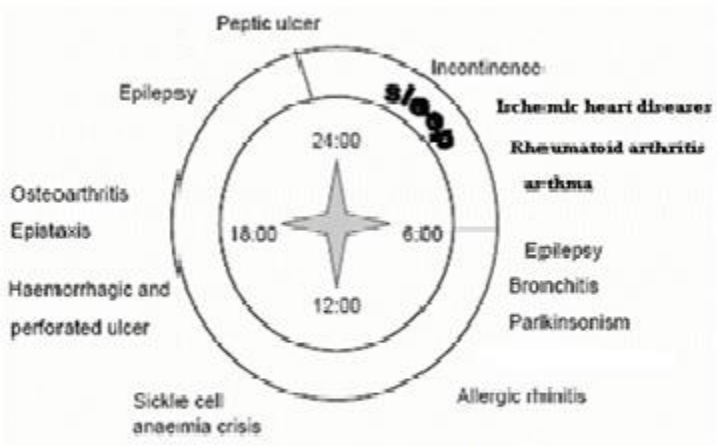

Fig1. Cycle of Circadian Rhythm

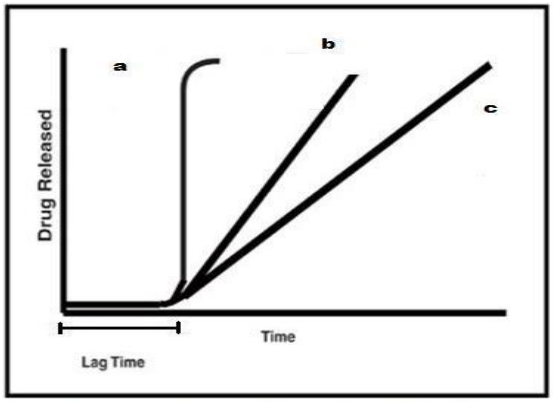

Fig2. Drug release proÞ les: (A) pulsatile (B) & (C) Conventional , Extended Release

EXPERIMENTAL MATERIAL AND METHODS

Two different methods have been investigated to induce the pulsatile release of therapeutic agents. One method is the elaboration of pre programmed delivery systems in which the drug is released at a predetermined time or in pulses of known sequence. A second method is the production of system that responds to specific stimuli.

Classification of Pulsatile Drug Dilevery System (PDDS)

PDDS is divided into two systems

A. Pre Planned System
B. Stimulus Induced Systems

A. Pre planned systems

1. Pulsatile system based on capsule
2. Pulsatile system based on osmosis
3. Drug delivery system with erodible or soluble layer
4. Drug delivery system with ruputrable layer

Pulsatile System Based On Capsule

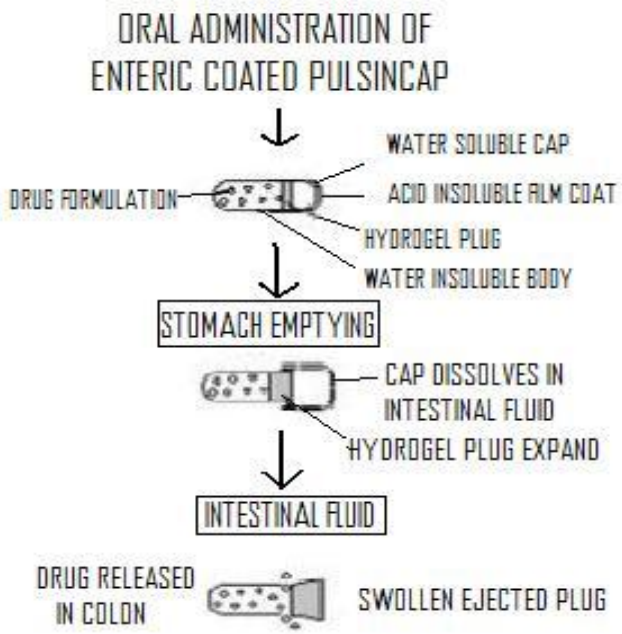

Fig 3. Pulsincap System

pushed itself outside the capsule and rapidly released the drug. Various types of material used for formulation of swellable plug which include hydroxyl propyl methl cellulose, poly vinyl acetate and poly ethylene oxide. The length of plug decides lag time.[5,6] There are another two approaches, one is generation of hydrostatic pressure by using biodegradable capsule of poly (lactic acid) (PLA) containing the drug along with citric acid / sodium bicarbonate and glucose was prepared. Thin poly (lactide-co-glycolide) (PLGA) membrane (to allow water penetration inside the capsule) was utilized on one end. Water penetrates into the capsule through the thin poly (lactide-co-glycolide) (PLGA) membrane side, which generates effervescence due to reaction caused between the citric acid and sodium bicarbonate, generating carbon dioxide gas. Onther approach is pulsincap for position

Capsule based system consists of pulsincap system, which consists of an insoluble capsule body and swellable and degradable plugs made of approved substances such as hydrophilic polymers or lipids (Krogel et al.1998; Krogel et al. 1999). The lag time is controlled by plug, which pushed away by swelling or erosion and drug is released as a pulse from the insoluble capsule i.e. Pulsincap®. A swellable hydrogel plug seals the drug contents in to capsule body. When this capsule body came in to contact with dissolution medium, the hydrogel plug swells, and after the lag time the plug

controlled pulsatile release [7] which ia achevied by using coatin membranes. One of the coating membranes is composed of an enteric polymer and the second membrane barrier is composed of a mixture of water-insoluble polymer and an enteric polymer. The composition and the thickness of the polymeric membranes determine the lag time and the duration of the drug release from each of the bead populations. In other preparations, an organic acid such as fumaric acid, citric acid, succinic acid, tartaric acid or malic acid, is included and a maleic acid containing membrane may be provided between the first and second membrane layers to provide for the time-separated pulses. The acids in between the membranes may delay the dissolution of the enteric polymer in the inner layer, thereby increasing the lag time as well as decreasing the rate of release of the active ingredient from the coated microparticulates. The enteric coating membrane is generally incorporated in the innermost layer to have the drug released in the lower intestine.

Pulsatile System Based On Osmosis

Osmotic system consists of capsule coated with the semipermiable membrane.In this system for development of osmotic pressure different techniques are used.

Case 1: *Osmotic system containing insoluble plug*, Osmotic system consists of capsule coated with the semipermiable membrane. Inside the capsule was an insoluble plug, osmotically active agent and the drug formulation. When this capsule came in contact with the body fluid, the semipermeable membrane.

Case 2: *Osmotic system based on expandable orifice technology*, Linkwitz *et al*. invented tThe system is in the form of capsule from which the drug is delivered by the capsule's osmotic infusion of moisture from the body. The delivery orifice opens intermittently to achieve pulsatile delivery effect. The orifice forms in the capsule wall, which is constructed of an elastic material, preferably elastomer (eg. Styrene-butadiene copolymer), which stretches under a pressure differential caused by the pressure rise inside the capsule.

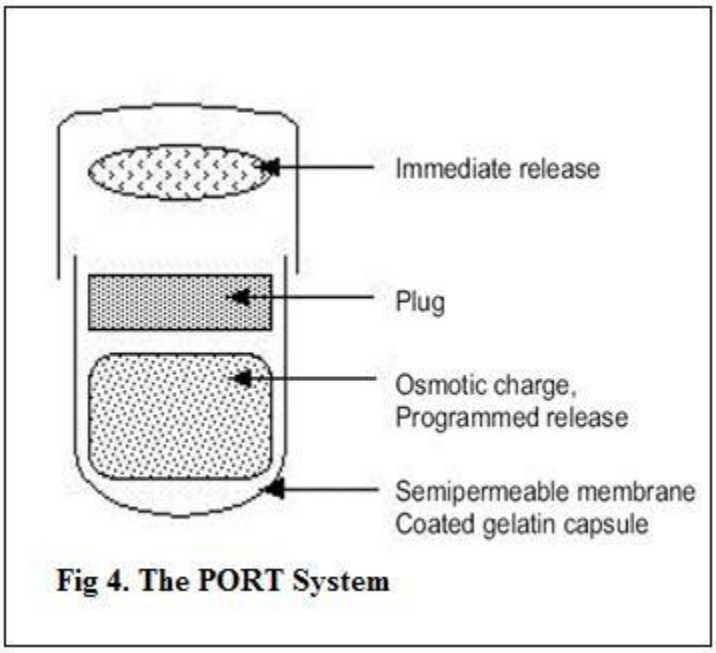

Fig 4. The PORT System

Case 3: *Osmotic capsule containing micropores*, *Niwa* et al. invented A novel capsule made from ethyl cellulose for time-controlled release of drugs in the colon.[11] Initially, the capsule was prepared by using a gelatin capsule with ethyl cellulose. The thickness of ethyl cellulose capsule body was varied and the effect of the wall thickness on the release of the drug in the capsules was investigated. The ethyl cellulose capsules contained a large number of mechanically made micropores (400 μm) at the bottom. A swellable layer consisting of lowsubstituted hydroxy propyl cellulose (L-HPC) was located in the bottom of capsule body. Above the swellable layer was the drug reservoir which contained mixture of model drug, fluorescein and a bulking agent, such as lactose and starch. The capsule was then capped and sealed with a concentrated ethyl cellulose solution. After administration of the drugcontaining capsule, water molecules penetrated the capsule through the micropores in the bottom of the capsule body. Hydration and swelling of the L-HPC induced an increase in the internal osmotic pressure, which resulted in the "explosion" of the capsule and a burst-like drug release was observed. The lag time of the drug release could be altered by altering the thickness of the capsule[9].

Drug Delivery System With Erodible Or Soluble Layer

In such systems the drug release is controlled by the dissolution or erosion of the outer coat which is applied on the core containing drug. Time dependent release of the active ingredient can be obtained by optimizing the thickness of the outer coat[10] e.g chronotropic system which consists of a drug containing core layered with HPMC optionally coated with an outer enteric coating. The lag time prior to drug release is controlled by the thickness and the viscosity grade of HPMC layer [11].

The time clock system is a delivery device based on solid dosage form that is coated by an aqueous dispersion[12]. This coating is a hydrophobic-surfactant layer to which a water-soluble polymer is added to improve adhesion to the

core. Once in contact with the dissolution fluid, the dispersion rehydrates and redisperses. The lag time could be controlled by varying the thickness of the film. This system has shown reproducible results *in vitro* and *in vivo*. The effect of low calorie and high calorie meal on the lag time was studied using gamma scintigraphy. The mean lag time of drug release was 345 and 333 min, respectively.

Pulsatile release tablet was developed that can suppress release of the drug in the stomach and can release the drug rapidly after a predetermined time of about 3 hrs in the intestine. The system consists of a core, swelling agent of cross linked PVP and a coating film of ethyl cellulose/ Eudragit L. Eudragit L dissolves in an environment of pH above 6 and creates pores in the coating film. Penetration of water molecules from the surroundings through the pores in to the core causes expansion of the swelling agent, bursting the film and releasing the drug with a single pulse. Manipulation of the thickness of coating film can control the lag time.

Drug Delivery System With Rupturable Layers/ Membranes

These systems consist of an outer release controlling water insoluble but permeable coating subject to mechanically induced rupture phenomenon. Recently different systems based on hard gelatin capsules and tablet core were described, all coated by inner swellable and outer rutpurable layer. The film rupture may be attained by including swelling, osmotic or effervescent additives in the reservoir[13].

Bussemer *et al.* worked on a pulsatile system with rupturable coating on drug present in hard gelatin capsules. These capsules were first coated with a swelling layer and then with an insoluble but water-permeable outer coating. These coated capsules when immersed in the release media could take up the media at a constant rate up to a point when the outer coating would rupture because of the pressure caused by the swelling layer. It could be concluded that by increasing the swelling layer, the lag time could be shortened. However, by increasing the outer coating, the lag time could be prolonged. It was also observed that addition of HPMC to the outer coating shortens the lag time[14].

A pharmaceutical implant was developed for biologically active material, an excipient comprising at least one watersoluble material and above which polymer film coating adapted to rupture at predetermined period of time after implantation[15] In one form, a bilayer film coating forms an impermeable barrier to the drug. An insoluble outer film controls the degree of access of physiological film to the inner film. A film coating comprising a mixture of ethyl cellulose and a copolymer of glycolic and lactic acids is used. As ethyl cellulose is an insoluble polymer, when the polylactic glycolic acid (PLGA) polymer in the film hydrolyses, the film becomes porous and allows release of the drug. The rate of hydrolysis of the PLGA depends on the ratio of the lactic acid to glycolic acid in the polymer.

The multi unit systems which produce more then one pulse are also possible and some companies like Eurand Ltd. are working this direction. Generally two or three pulse creations are possible. Almost erodible layer and rupturable layer system are used for more than one pulse creation and are almost same like the single unit system described above.

B. STIMULI INDUCED PULSATILE SYSTEMS

I. *Temperature induced system*

II. *Chemically induced System*

III. *Externally induced System*

I. Temperature Induce System

Thermo-responsive hydrogel systems have been developed for pulsatile release. In these systems the polymer undergoes swelling or deswelling phase in response to the temperature which modulate drug release in swollen state[16]. Y.H. Bae et al developed indomethacin pulsatile release pattern in the temperature ranges between 200C and 300C by using reversible swelling properties of copolymers of N-isopropylacrylamide and butyrylacrylamide. Kataoka et al developed the thermosensitive polymeric micelles as drug carrier to treat the cancer. They used endfunctionalized poly(*N*-isopropylacrylamide) (PIPAAm) to prepare corona of the micelle which showed hydration and dehydration behavior with changing temperature[17].

II. Chemically Induced System

There has been much interest in the development of stimuli-sensitive delivery systems that release a therapeutic agent in presence of specific enzyme or protein. One prominent application of this technology has been development of a system that can autonomously release insulin in response to elevated blood glucose levels. Several existing strategies that may be feasible for glucose-responsive drug delivery are discussed below: pH-dependent systems for Glucose stimulated drug delivery are based on the reaction that glucose oxidase catalyses oxidation of glucose to gluconic acid. This reaction can be used to drive the swelling of pH-dependent membrane. A dual membrane system was formed. In the first membrane, glucose oxidase was immobilized on cross linked polyacrylamide and this was referred to as glucose sensing membrane. Co-polymer membrane composed of N, N-diethylaminoethyl methacrylate and 2-hydroxypropyl methacrylate (DEA-HPMA) formed the barrier membrane and worked as an interface between insulin reservoir and sensing membrane[18].

In pH sensitive system there are two components one is of immediate release type and other one is pulsed release which releases the drug in response to change in pH. In case of pH dependent system advantage has been taken of the fact that there exists different pH environment at different parts of the gastrointestinal tract. By selecting the pH dependent polymers drug release at specific location can be obtained. Examples of pH dependent polymers include cellulose acetate phthalate, polyacrylates, and sodium carboxymethyl cellulose. These polymers are used as enteric coating materials so as to provide release of drug in the small intestine. Yang et al developed pH-dependent delivery system of nitrendipine in which they have mixed three kinds of pH dependent microspheres made up of acrylic resins Eudragit E-100, Hydroxypropylmethylcellulose phthalate and Hydroxypropylmethylcellulose acetate succinate as pH dependent polymers. In one of the study carried out by Mastiholimath et al attempt was made to deliver theophylline into colon by taking the advantage of the fact that colon has a lower pH value (6.8) than that of the small intestine (7.0–7.8). So, by using the mixture of the polymers, i.e. Eudragit L and Eudragit S in proper proportion, pH dependent release in the colon was obtained[24]

Table 1. Marketed Technologies of Pulsatile Drug Delivery System

Technology	Mechanism	API	Disease	Reference
Pulsys®	Timed-controlled System	Amoxicillin	pharyngitis/tonsillitis	27
Uniphyl®	Externally regulated System	Theophylline	Asthma	27
Ritalina®	Osmotically regulated	Methyl Phenidate	Attention Deficit Hyperactivity Disorder	27
Opana®ER	Timed-controlled System	Oxymorphone	Pain medicine	28
TheirForm®	Externally regulated system	Diclofenac sodium	Inflammation	29

III. Externally Stimuli System

For releasing the drug in a pulsatile manner, another way can be the externally regulated systems in which drug release is programmed by external stimuli like magnetism, ultrasound, electrical effect and irradiation.

1. Magnetically Stimulated

Saslawski *et al.*[19] developed different formulations for in vitro magnetically triggered delivery of insulin based on alginate spheres. In an experiment, ferrite microparticles (1µm) and insulin powder were dispersed in sodium alginate aqueous solution. The ferrite-insulin alginate suspension was later dropped in aqueous calcium chloride solution which causes the formation of cross linked alginate spheres, which were further cross linked with aqueous solution of poly(L-lysine) or poly(ethylene imine). They described that the magnetic held characteristics due to the ferrite microparticles and the mechanical properties of the polymer matrices could play role in controlling the release rates of insulin from the system. US Patent 2006 997863[20] provides 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 tumor or cancer cells.

2. Ultrasonically Stimulated

Ultrasound is mostly used as an enhancer for the improvement of drug permeation through biological barriers, such as skin, lungs, intestinal wall and blood vessels. There are several reports describing the effect of ultrasound on controlled drug delivery. Kost *et al.* described an ultrasound-enhanced polymer degradation system. During polymer degradation incorporated drug

molecules were released by repeated ultrasonic exposure. As degradation of biodegradable matrix was enhanced by ultrasonic exposure, the rate of drug release also increased. Thus, pulsed drug delivery was achieved by the on-off application of ultrasound[21]. Miyazaki et at. [22] used ultrasound to achieve up to a 27-fold increase in the release of 5-fluorouracil from an ethylene and vinyl acetate (EVAc) matrix.Increasing the strength of the ultrasound resulted in a proportional increase in the amount of 5-fi uorouracil released.

3. Photo Stimulated

The interaction between light and material can be used to modulate drug delivery. This can be accomplished by combining a material that absorbs light at a desired wavelength and a material that uses energy from the absorbed light to modulate drug delivery. Embedding the nanoshells in a NIPAAm-co-AAM hydrogel formed the required composite material. When exposed to near-infrared light, nanoshells absorb the light and convert it to heat, raising the temperature of composite hydrogel above its LCST. That's result in the increase rate release of the drug from matrix system[23].

4. Electrically stimulated

An electricfield as an external stimulus has advantages such as availability of equipment, which allows precise control with regards to the magnitude of the current, duration of electric pulses, interval between pulses etc. Electrically responsive delivery systems are prepared from polyelectrolytes and are thus pH- responsive as well as electro responsive. Under the infi uence of electric › eld, electro responsive hydrogels generally deswell, swell or erode. Poly(2-acrlamide-2-methylpropanesulfonic acid-co-butyl methacrylate) (P(AMPS-co-BMA) hydrogels were used for electric stimuli-induced drug delivery system[25,26]. Positively charged edrophonium chloride was incorporated as drug molecule within negatively charged P(AMPS-co-BMA) hydrogels. By applying an electric › eld, ion exchange between edrophonium ions and protons commenced at cathode, resulting in rapid drug release from hydrogels. This rapid drug release was attributed to the electrostatic force, squeezing effect, and electro-osmosis of the gel. Complete on-off drug release was achieved, as no drug release was apparent without the application of electric current.

MODERN DEVELOPMENT ON PULSATILE SYSTEM Nowadays pulsatile drug delivery systems are gaining importance in various disease conditions specifically in diabetes where dose is required at different time intervals. Among these systems, multi-particulate systems (e.g. pellets) offer various advantages over single unit which include no risk of dose dumping, flexibility of blending units with different release patterns, as well as short and reproducible gastric residence time. Multiparticulate systems consists pellets of different release profile which can be of any type like time dependent, pH dependent, micro flora activated system as discussed in the previous sections. Site and time specific oral drug delivery have recently been of great interest in pharmaceutical field to achieve improved therapeutic efficacy. Gastroretentive drug delivery system is an approach to prolong gastric residence time, thereby targeting sitespecific drug release in upper gastrointestinal (GI) tract. Floating drug delivery system (FDDS) and bioadhesive drug delivery are widely used techniques for gastro retention. Low density porous multiparticulate systems have been used byresearchers for formulation of FDDS. Sharma and Pawar developed multiparticulate floating pulsatile drug delivery system using porous calcium silicate and sodium alginate for time and site specific drug release of meloxicam. Various pulsatile technologies have been developed on the basis of methodologies as discussed previously. These includes OROS® technology, CODAS® technology, CEFORM®

technology, DIFFUCAPS® technology, Three-dimensional printing®, timerx® etc. Table.2 summarizes the technologies of pulsatile drug delivery.

CONCLUSION

There is a constant need for new delivery systems that can provide increased therapeutic benefits to the patients. Circadian rhythm of the body is an important concept for understanding the optimum need of drug in the body. Pulsatile drug delivery is one such system that, by delivering drug at the right time, right place & in right amounts, holds good promises of benefit to the patients suffering from chronic problems like arthritis, asthma, hypertension, etc.Thus, designing of proper pulsatile drug delivery will enhance the patient compliance, optimum drug delivery to the target side & minimizing the undesired effects.

REFRENCES

1. Davis S.S. , Illum L., " Drug delivery systems for challenging molecules". Int. J. pharm., 176 , 1998, 1-8.
2. Rubinstein A, Tirosh B, Baluom M, Nassar T, David A, "The rationale for peptide drug delivery to the colon and the potential of polymeric carriers as effective tools", J. Controlled Release 46 , 1995,59-73.
3. 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, 99-108
4. Ronald A. S., Colin G. P. , "A strategy for oscillatory drug release general scheme and simplified theory" , J. Controlled Release 33 , 1995, 173-188
5. Krogel I., Bodmeir R. , "Pulsatile drug release from an insoluble capsule body controlled by erodible plug", Pharm Res 15, 1998, 474-81.
6. Krogel I., Bodmeir R., "Evaluation of enzyme-containing capsular shaped pulsatile drug delivery system" , Pharm Res. , 142, 1999, 4-9.
7. Percel P., Vishnupad K.S. , Venkatesh G.M. , "Timed pulsatile drug delivery system", US6627223B2, 2003.
8. Linkwitz A., Magruder J.A., Merrill S., ". Osmotically driven delivery device with expandable orifice for pulsatile delivery effect" , US Patent No. US5318558, 1994.
9. Niwa K., Takaya T., Morimoto T., Takada K., " Preparation and evaluation of time controlled release capsule made of ethyl cellulose for colon delivery of drugs" , J. Drug Targeting 38, 1995 , 3-9.
10. Gazzaniga A, Paluga L, Foppoli A, Maria E.S., "Oral pulsatile delivery systems based on swellable hydrophilic polymers" , Euro. J. Pharma. And Biopharm. , 68 , 2008 , 11-18. Maroni A., Zema L., Cerea M., Sangalli M.E., "Oral pulsatile drug delivery systems". Exp Opin Drug Deliv 28, 2005, 55-71.
11. Sangalli M.E., Maroni A., Zema L., Busetti C., Giordano F., Gazzaniga A., "In vitro and in vivo evaluation of an oral system for time and/or site-specific drug delivery" , J. Controlled Release, 73 , 2001 , 103-110.
12. Krögel I., Roland B., "Floating or pulsatile drug delivery systems based on coated effervescent cores", Int. J. Pharm., 187 , 1999 , 175-184.
13. Krögel I. , Bodmeier R. , "Floating or pulsatile drug delivery systems based on coated effervescent cores" , Int. J. Pharma. 187 , 1999 , 175-184.
14. Bussemer T. , Dashevsky A., Bodmeier R., "A pulsatile drug delivery system based on rupturable coated hard gelatin capsules", 93 , 2003 , 331-339.
15. Barr I.G., Thiel W.J., "Single dose vaccination system", US patent no. US5593697, 1997
16. Kikuchi A., Okano T., "Pulsatile drug release control using hydrogels", Adv. Drug Del. Rev. , 54 , 2002 , 53-77
17. Kataoka K., Harada A., Harada A., Nagasaki Y., "Block copolymer micelles for drug delivery: design, characterization and biological significance", Adv. Drug Del. Rev., 47 , 2001 , 113-131
18. Ishihara K., Kobayashi M., Ishimura N., Shinohara I., "Glucose Induced Permeation Control of Insulin through a Complex Membrane Consisting of Immobilized Glucose Oxidase and a Poly(amine)", Polymer J. , 16, 1984, 625-631.

19. Saslawski O., Weigarten C., Beniot J.P., Couvereur P., "Magnetically responsive microspheres for the pulsed delivery of insulin", Life Sci., 42 , 1988 , 1521-1528.
20. Handy E.S., Ivkov R., Ellis-Busby D., Forman A., Braunhut S.J., Gwost D.U.,Ardman B., "Thermo therapy via targeted delivery of nanoscale magnetic particles" , US Patent No. US997863,2006.
21. Supersaxo A., Kou J.H., Teitelbaum P., Maskiewicz R., "Preformed porous microspheres for controlled and pulsed release of macromolecules", J. Controlled Release, 23, 1993, 157-164
22. Kost J., "Ultrasound for controlled delivery of therapeutics", Clinical Materials , 13, 1993,155-161.
23. Averitt R.D., Sarkar D. and Halas N.J., "Plasmon Resonance Shifts of Au-Coated Au_2S Nanoshells: Insight into Multicomponent Nanoparticle Growth", Phys. Rev. Lett.,78 1997, 4217-4220.
24. Mastiholimath V.S., Dandagi P.M., Samata S.J, Gadad A.P., Kulkarni A.R. , "Time and pH dependent colon specific, pulsatile delivery of theophylline for nocturnal asthma", Int. J. Pharma., 328 , 2007 , 49-56
25. Kwon, I.C., Bae, Y.H., Okano, T., Berner, B., and Kim, S.W., "Electrically credible polymer gel for controlled release of drugs" , Makromol Chem. Makromol. Symp., 33 1990 , 265-277.
26. Yoshida R., Kaneko Y., Sakai K., Okano T., Sakurai Y., Bae Y.H., Kim S.W.,"Positive thermosensitive pulsatile drug release using negative thermosensitive hydrogels" J. Control. Released , 32 , 1994 ,97-102.
27. http://www.authorstream.com/Presentation/abikesh086-235605-pulsatile-drug-delivery system-education-ppt-powerpoint/
28. http://www.opana.com/hcp/opana-er/durability/
29. Katstra W.E, Palazzolo R.D.,Rowe C.W., Giritlioglu B., Teung P., Cima M.J. , "Oral dosage forms fabricated by Three Dimensional Printing™", J. Controlled Release , 66 , 2000, 1-9.

Authors Address for communication:

Jigar D Patel

School of Pharmacy & Technology Management, SVKM's NMIMS University, Babulde Bank of Tapi River, Mumbai-Agra Road,
Shirpur, Dist. Dhule-425405 (Maharashtra)

Phone No.:- 09373524653

E-mail:- jigarpatel31187@gmail.com