ISSN: 0975-766X
Review Article

Available Online through
www.ijptonline.com

PULSATILE DRUG DELIVERY SYSTEM: A REVIEW AN ADVANCED APPROACH

Shiwani Sharma*[1], Anshul Dutt Sharma[1], Roopa Saharawat[2]
[1]Adarsh Vijendra Institute of Pharmaceutical Sciences, Gangoh, Saharanpur, U.P, 247341.
[2] Himalayan Institute of Pharmaceutical Sciences, Kalamb, H. P, 173030.
Email: shivani86vats@gmail

Received on 12-05-2011 *Accepted on 25-05-2011*

Abstract:

Oral administration of different dosage forms is the most commonly used method due to greater flexibility in design of dosage form and high patient acceptance, but the gastrointestinal tract presents several barriers to drug delivery. Different approaches are designed based on prodrug formulation, pH-sensitivity, time-dependency (lag time), microbial degradation and osmotic pressure etc to formulate the different dosage forms like tablets, capsules, multiparticulates, microspheres, liposomes for improving such problems. Our aim in this review is to outline the rational and prominent design strategies behind site-specific oral pulsatile delivery. The present article provides a good review regarding the Site Specific Drug Delivery system. These pulsatile drug delivery system(P.D.D.S) are better than traditional sustained drug delivery systems(D.D.S).These systems release drugs on a programmed pattern means at appropriate time and/or at appropriate site of action

Keywords: Pulsatile release, chronotherapeutics, time controlled systems, Pulsatile drug delivery

Introduction:

Conventional controlled release drug delivery systems are based on single- or multiple-unit reservoir or matrix systems, which are designed to provide constant or nearly constant drug levels over an extended period of time[1,2]. However, pulsatile delivery is desirable for drugs acting locally or having an absorption window in the gastro-intestinal tract or for drugs with an extensive first pass metabolism, e.g. β- blockers or for drugs, which develop biological tolerance, where the constant presence of the drug at the site of action diminishes the therapeutic effect, or for drugs with special pharmacokinetic features designed according to the circadian rhythm of human [3, 4].Circadian rhythms are self-sustaining, endogenous oscillations that occur with a periodicity of

about 24 Hours[5]. Coordination of biological rhythms and medical treatment is called chronotherapy while chronotherapeutics is the discipline concerned with the delivery of drugs according to inherent activities of a disease over a certain period of time[6]. Many systems in the human body such as cardiovascular, pulmonary, hepatic and renal systems how variation in their function throughout a typical day. They are naturally synchronized by the internal body clocks and are controlled by the sleep wake cycle. Each bodily system exhibits a peak time of functionality that is in accordance with these rhythmical cycles. Similarly, disease states affect the function of some of these systems in the body and therefore, they too exhibit a peak time of activity within a circadian rhythm[7]. A delivery system with a pulsatile release profile where the drug is released completely after a defined lag time, is called as an ideal pulsatile drug delivery system. In other words, it is required that a drug should not be released at all during the initial phase of dosage form administration[8,3].

Advantages of P.D.D.S

1. A pulsatile release profile is advantageous for several drugs or therapies,where the drug is released completely after a defined lag time.
2. For drugs which develop biological tolerance,
3. For drugs with an extensive first pass metabolism,
4. For drugs targeted to a specific site in the intestinal tract, e.g. to the colon, protecting the drug from degradation .
5. Chronopharmacotherapy of diseases which shows circadian rhythms in their pathophysiology
6. For time programmed administration of hormone and drugs.
7. For drugs having the short half life.
8. Capsular-shaped systems are more independent from the nature of the content, for example, the Pulsincap system which consists of an insoluble capsule body and a swellable plug.[9-12].

Diseases cured BY P.D.D.S

Diseases where rhythmic circadian organization of the body plays an important role, Pharmacokinetics and/or pharmacodynamics of the drugs is not constant within 24 h can be cured by using P.D.D.S.

Examples of diseases cured by P.D.D.S

Peptic ulcer this disease is effected by circadian rhythm of body and Acid secretion is high in the afternoon and at night.

Asthma circadian rhythm also have effect on this disease as Precipitation of attacks occurs during night or at early morning hours.

Cardiovascular diseases BP is at its lowest during the sleep cycle and Nitroglycerin, Calcium channel rises steeply during the early morning awakening period.

Arthritis Pain in the morning and more pain at night.

Diabetes mellitus Increase in the blood sugar level after meal.

Attention deficit syndrome Increase in DOPA level in afternoon

Hypercholesterolemia Cholesterol synthesis is generally higher HMG CoA reductase inhibitors during night than during day time[13-14].

Constitution OF P.D.D.S

Constitution of active core:

Active core of the novel dosage form may comprise an inert particle such as a sugar sphere or a cellulose sphere with a desired mean particle size. Alternatively, drug- containing cores (microgranules, pellets or micro-tablets) may be prepared by rotogranulation, granulation followed by extrusionspheronization or compression into micro-tablets (about 1 to 2 mm in diameter) of the drug, a polymeric binder and optionally fillers/diluents. The drug load in the cores could be as high as 60 percent by weight in drug-layered beads and as high as 95 percent in pellets and micro-tablets.

Solvent Medium:

An aqueous or a pharmaceutically acceptable solvent medium (e.g. water or acetone/water) may be used for preparing core particles, and the drug substance may be dissolved or suspended in this coating formulation at a solid content of about 10 to 30 percent by weight depending on the viscosity of the coating formulation. Generally, the individual polymeric coating applied on the active cores from a solution or an aqueous suspension

will vary from about 1.5 to 60 percent by weight depending on the nature of the active and required sustained release duration[15].

CLASSIFICATION OF P.D.D.S DEPENDING UPON TARGET RELEASE

Site-Specific Systems

The drug in such systems is released at the desired site within the intestinal tract (e.g., the colon). Environmental factors like pH or enzymes present in the intestinal tract control the release of a site-controlled system.

Time-Controlled Devices

The drug in such systems is released after a well-defined time period. The drug release from time-controlled systems is controlled primarily by the delivery system and not by the environment[16]. In time controlled drug delivery systems pulsatile release is obtained after a specific time interval in order to mimic the circadian rhythm. Such type of pulsatile drug delivery system contains two components: one is of immediate release type and other one is a pulsed release type. Various methodologies such as time controlled devices with rupturable coating layer, erodible coating layer can be used for time controlled pulsatile devices.[17-19]

Stimuli induced pulsatile systems

In these systems there is release of the drug after stimulation by any biological factor like temperature,or any other chemical stimuli[20]. These systems are further classified in to temperature induced systems and chemical stimuli induced system, on the basis of stimulus.

Temperature induced systems

Thermo-responsive hydrogel systems have been developed for pulsatile release. In these systems polymer undergoes swelling or deswelling phase in response to the temperature which modulate drug release in swollen state[21]

Drug release from intelligent gels responding to antibody concentration

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

polymerized antibodies and naturally derived antibodies towards specific antigens, reversible gel swelling/deswelling and drug permeation changes occurs [22]

PH sensitive drug delivery system

Such type of pulsatile drug delivery system contains 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 includes cellulose acetate phthalate, polyacrylates, sodium carboxymethylcellulose. These polymers are used as enteric coating materials so as to provide release of drug in the small intestine[23].

Externally regulated systems

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[24].

CLASSIFICATION OF P.D.D.S DEPENDING UPON TECHNOLOGY USED

From technological point of view pulsatile drug release system are further divided to single or multiple units system.

Single Unit System:

Single unit system can be of following types:

Capsule Based

Such type of drug delivery system for administering a drug in controlled pulse doses to an aqueous environment in the body of a living being. The formulation comprises of one or more, and preferably less than ten, individual drug-containing subunits in a unitary drug depot, such as a tablet or capsule. The individual subunits are designed to dissolve at different sites and/or times in the gastrointestinal tract to release pulse doses of drug into the portal system in an analogous manner to the rate of release from an immediate release dosage form administered according to an appropriate dosing schedule. The dissolution time of the individual subunits can be

controlled by several methods including the provision of pHsensitive enteric coatings and permeability-controlled coatings[25].

Osmosis Based

Osmotic delivery capsules ("osmotic pumps") function by virtue of walls which selectively pass water into the capsule reservoir. Absorption of water by the capsule through these walls is driven by a water-attracting agent in the capsule interior which creates osmotic pressure across the capsule wall. The water-attracting agent may be the beneficial agent itself whose controlled release is sought, but in most cases, it is a separate agent specifical1y selected for its ability to draw water, and this separate agent is being isolated from the beneficial agent at one end of the capsule[26].

Eroding/Soluble Barrier System

Such a system uses the degradation products of one polymer to trigger the release of the active compound from another polymer. The delayed release of the active compound is achieved without using a barrier system that requires complex and sophisticated formulation techniques. The proposed formulation comprises the biologically active compound having a chemical structure with hydrogen bonding sites dispersed in a biocompatible, hydrolytically degrading polyarylate. Bonding interactions between the polymer and the active compound are used to lock the active compound into the polymeric matrix. In order to control the time of release from polyarylates, a second biocompatible polymer but less hydrophobic than polyarylates is also used. The second polymer can be degraded into acidic byproducts into the matrix. This is necessary because the hydrogen bonding interactions can be weakened under conditions of low pH, resulting in the release of the peptide.Degradation products lower the pH of the matrix, causing an interruption in the interactions and the subsequent release of active compound[27].

Rapturable Layers

Mehta described a novel formulation for once daily administration (prior to sleeping) that provides an initial delay followed by controlled release of the drug. A method for preparing a time specific delayed, controlled release formulation of dosage is also provided which method includes coating a single pellet with at least one dosage layer, which is coated by at least one seal coat and at least one outer rate controlling layer of a water

soluble polymer coat. The formulation affords excellent bioavailability while avoiding fluctuating blood levels. By that way, it is possible to maintain drug plasmatic concentrations in a desired, effective range in a circadian fashion while simplifying the administration of the drug to only once daily[28].

Multiple Unit System:

Multiple unit system can be of following types:

Systems Based on Change in Membrane Permeability

In such kind of formulation of a multiparticulate pharmaceutical form of a delayed and/or pulsed release, enabling to obtain the onset of the availability of the active ingredient within 4 to 8 hours after the ingestion of the pharmaceutical form, and then a progressive release of the totality of the active ingredient within the 8 to 20 following hours. The formulations is in the form of spheroids consisting of a neutral spherical core comprising a first coating based on a mixture of at least one hydrosoluble polymer and of at least one non hydrosoluble polymer throughout which the constitutive particles of an active ingredient are uniformly distributed. A second coating based on at least two pH independent polymers presenting rates of permeability different from one another with respect to the gastric and intestinal mediums, was also used[29].

Systems with Rapturable Coating

Blum described a controlled release oral dosage form of acetylsalicylic acid (aspirin) capable of delaying the release of the drug until a predetermined time interval after ingestion. The following is prepared in such a manner that, after ingestion, there will be no release for a preset time interval (5-8 hours). Thus, if taken at bedtime it reaches optimal therapeutic blood levels at a time in the early morning when the events leading up to a vascular obstruction culminating in a heart attack or stroke are most commonly occurring after the drug is taken in the evening. The formulation comprises of an aspirin core together with a swelling agent and a frangible coating protecting aspirin from dissolution by gastrointestinal fluids having water soluble and insoluble properties[30].

Miscellaneous pulsatile systems

Some really novel systems of pulsatile release has also been proposed. For example, Weinbach and coworkers described a delayed release oral formulation (a capsule, tablet, compression coated tablet or bilayer tablet)

comprising at least two populations of carrier particles where the first population comprises a biologically active substance and a penetration enhancer (absorption enhancer), and the second population comprises a penetration enhancer and a delayed release coating or matrix. The first population is released from the formulation at a first location in the intestine and quickly release the biologically active substance and the penetration enhancer. The penetration enhancer promotes absorption of the biologically active substance; however, because the enhancer is quickly absorbed, there is often an insufficient amount of enhancer to promote absorption of the entire dose of biologically active substance. The second population of carrier particles comprise an enteric outer coating which resists degradation in the stomach and dissolves in the intestinal lumen and thus it is effective in protecting the nucleic acid from pH extremes of the stomach, or in releasing the nucleic acid over time to optimize the delivery thereof to a particular mucosal site[31].

Current & future developments

Currently 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[32]. Pulsatile-release formulations have many advantages over immediate-release formulations. With these formulations, frequent drug administrationcan be avoided, and patient compliance can correspondingly be improved. In the field of drug delivery, increased attention has recently been focused on the potential of systems that are able to release drugs after a programmable lag phase commencing at administration time, i.e., in a pulsatile mode. During the last two decades, technologies to ensure time-controlled pulsatile release of bioactive compounds have been developed. The future of chronotherapeutics and more specifically the future of delivering drugs in a pulsatile manner seem to be quite promising as in certain disease states pulsatile release exhibit several advantages over the traditional zero or first order drug delivery mechanisms. Pulsatile drug delivery systems can be either time controlled or site-specific, single or multiple units. At the moment pulsatile release (site or time specific) most often is achieved by using different polymers in coating layers or by changing the coating thickness. From technological point of view, multiparticulate systems seem to be more efficient than single-unit dosage forms in achieving pulsatile drug delivery and it can become even more sophisticated when coating technologies are incorporated. The authors of this paper believe

that an increasing number of multiparticulate coated systems would become commercially available in the years to come.

References

1. Daumesnil R. Marketing considerations for multiparticulate drug delivery systems. In: Ghebre-Sellassie, editors.Multiparticulate Oral Drug Delivery, Marcel Dekker, New York, 1994, pp 457– 474.
2. Qiu Y, Zhang G. Research and development aspects of oral controlled-release dosage forms. Wise DL, editor. In: Handbook of Pharmaceutical Controlled Release Technology, Marcel Dekker, New York, 2000, pp 465–504.
3. Rouge N, Buri P, Doelker E. Drug absorption sites in the gastrointestinal tract and dosage forms for site-specific delivery. Int. J. Pharm. 1996; 136: 117– 139.
4. Lemmer B. Chronopharmacokinetics: implications for drug treatment. J. Pharm. Pharmacol. 1999; 51: 887–890.
5. Jha N, Bapat S, Chronobiology and chronotherapeutics. Kathmandu Uni. Med. J.2004; 2 (8): 384-388.
6. Peppas NA, Leobandung W. Stimuli-sensitive hydrogels: ideal carriers for chronobiology and chronotherapy. J Biomat Sci Polym. 2004; 15: 125-144.
7. Jason T. Recent trends in oral drug delivery. Drug Deliv Report Autumn/Winter. 2005; 24-27.
8. Ayres JW.: US20046733784. 2004.
9. Chen X , Jun Shou Z, Yun MO. Calcium pectinate capsule for colon specific drug delivery. Drug Dev. Ind. Pharm. 2005; 31:127–134.
10. Chourasia MK, Jain SK. Pharmaceutical approaches to colon targeted drug delivery systems. J. Pharm. Pharmaceut.Sci. 2003; 6: 33–66.
11. Zhang Z, Wu F, Zhang Y. A novel pulsed-release system based on swelling and osmotic pumping mechanism, Journal of Controlled Release. 2003; 89: 47–55.
12. Bikiaris D, Karavas E, Georgarakis E. Application of PVP/HPMC miscible blends with enhanced mucoadhesive properties for adjusting drug release in predictable pulsatile chronotherapeutics, Eur. J. Pharm and Biopharm. 2006; 64: 115–126.

13. Hermida RC, Ayala DE, Calvo C, Adv. Drug Del. Rev. 2007.

14. Lemmer J. Control. Rel. 1991; 16: 63-74.

15. Gazzaniga A, Palugan L, Foppoli A, Sangalli ME. Oral pulsatile delivery systems based on swellable hydrophilic polymers. Eur J Pharm Biopharm 2008; 68: 11-18.

16. Saigal N, Ali J, Ahuja A, Babbota S. Site Specific Chronotherapeutic Drug Delivery Systems: A Patent Review. Recent Patents on Drug Delivery & Formulation 2009;3: 64-70.

17. Thombre AG, Appel LE, Chidlaw MB. J. Control. Rel 2004; 94:75-89.

18. Gazzaniga A, Paluga L, Foppoli A. Eur. J. Pharm. and Biopharm 2007.

19. Sangalli ME, Maroni A, Foppoli A. European Journal of Pharmaceutical Sciences 2004; 22: 469-476.

20. Siegel RA, Pitt CG. J. Control. Rel 1995; 33:173-188.

21. Kikuchi A, Okano T. Adv. Drug Del. Rev. 2002; 54: 53-77.

22. Miyata T, Asami N, Uragami T . Nature 1999; 3: 766-769.

23. Mastiholimath VS, Dandagi PM, Jain SS. Int. J. pharm 2007; 328:49-56.

24. Saslawski O, Weigarten C, Benoit JP. Life Sci 1988; 42:1521.

25. Amidon GL, Leesman GD. US5229131. 1993.

26. Magruder PR, Barclay B. US4777049. 1988.

27. Kohn JB, Schachter DM. US20067326425. 2006.

28. Mehta AM. US20056926909. 2005.

29. Gendrot E, Cousin G, Ragot F, Clee-Bouvet MC.US20036039979. 2003.

30. Blum AS. US20036663896B1. 2003.

31. Weinbach S, Tillman LG, Geary RS, Hardee GE. US2005196443. 2005.

32. Sharma S, Pawar A. Int. J. pharm. 2006; 313.

Corresponding Author:

Shiwani Sharma*,

Email: *shivani86vats@gmail.com*