ISSN: 2320 - 4230

Journal of Drug Discovery and Therapeutics 1 (4) 2013, 15-22

REVIEW ARTICLE

COMPREHENSIVE REVIEW ON PULSATILE DRUG DELIVERY SYSTEM

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ABSTRACT

Oral controlled drug delivery systems represent the most popular form of controlled drug delivery systems for the obvious advantages of oral route of drug administration. However, there are certain conditions for which such a release pattern is not suitable like cardiovascular diseases, Diabetes mellitus, Asthma, Arthritis, Peptic ulcer etc. In such cases pulsatile drug delivery system is used in which release drug on programmed pattern i.e. at appropriate time & at appropriate site of action. Pulsatile Drug Delivery systems are basically time controlled drug delivery systems in which the system controls the lag time independent of environmental factors like pH, enzymes, gastrointestinal motility, etc. The principle rationale for the use of pulsatile release is for the drugs where a constant drug release, i.e., a zero-order release is not desired. In chronopharmaco therapy drug administration is synchronized with biological rhythms to produce maximal therapeutic effect & minimum harm for the patient. Technically, pulsatile drug delivery systems administered via the oral route could be divided into two distinct types, the time systems and the site-specific delivery systems, thus providing special and temporal delivery. In recent pharmaceutical applications involving pulsatile delivery; multiparticulate dosage forms (e.g. pellets) are gaining much favor over single-unit dosage forms. Designing of proper pulsatile drug delivery will enhance the patient compliance, optimum drug delivery to the target side & minimizing the undesired effects.

KEY WORDS: Pulsatile Drug Delivery, Chronotherapeutics, Time Controlled Systems, pH target release.

INTRODUCTION:

Oral controlled drug delivery systems represent the most popular form of controlled drug delivery system for the more obvious advantage of the oral routes of the administration. Such systems release the drug with constant or variable release rates. These dosage forms offer many advantages, such as nearly constant drug level at the site of action, prevention of peak-valley fluctuations, reduction in dose of drug, reduced dosage frequency, avoidance of side effects, and improved patient compliance However, there are certain conditions for which such a release pattern is not suitable. These conditions demand release of drug after a lag time.

In other words, it is required that the drug should not be released at all during the initial phase of dosage form administration. Such a release pattern is known as pulsatile release.

The principle rationale for the use of pulsatile release is for the drugs where a constant drug release, i.e., a zero-order release is not desired. The release of the drug as a pulse after a lag time (an interval of no drug release) has to be designed in such a way that a complete and rapid drug release follows the lag time. In chronopharmacotherapy (timed drug therapy) drug administration is synchronized with biological rhythms to produce maximal therapeutic effect and minimum harm for the patient. By basing drug delivery on circadian patterns of Diseases, drug effect can be optimized and side effects can be reduced. If symptoms occur at daytime a conventional dosage form can be administered just prior the symptoms are worsening. If symptoms of a disease became worse during the night or in the early morning the timing of drug administration and nature of the drug delivery system need careful consideration. Pulsatile release is also useful for the targeting of the drug irritating the stomach or degradable therein, as well for drugs developing biological tolerance or with an extensive first-pass metabolism[1].

CHRONOPHARMACOTHERAPY:

Recent studies show that diseased have predictable cyclic rhythms and the timing of medication regimens can improve outcome in selected chronic conditions. "Chronopharmaceutics" consist of two words chronobiology and Pharmaceutics[2]. Chronobiology is the study of biological rhythms and their mechanisms. There are three types of mechanical rhythms in our body, they are:

- Circadian
- Ultradian
- Infradian

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1. Ultradian Rhythms:
Oscillations of shorter duration are termed Ultradian Rhythms (more than one cycle per 24 h). E.g. 90 minutes sleep cycle[3]

2. Infradian Rhythms:
Oscillations that are longer than 24 hours are termed as Infradian Rhythms (less than one cycle per 24hours). E.g. Monthly Menstruation[3]

3. Circadian Rhythms:
Circadian rhythms are self-sustaining, endogenous oscillations that occur with a periodicity of about 24 Hours. Interestingly, the term circadian is derived from the Latin circa which means "about" and dies which can be defined as "a day". Normally, circadian rhythms are synchronized according to internal biologic clocks related to the sleep-wake cycle[3].

DISEASES AND CHRONOTHERAPEUTICS:

The potential benefits of chronotherapeutics have been demonstrated in the management of a number of diseases. In particular there is a great deal of interest in how chronotherapy can particularly benefit patients suffering from allergic rhinitis, rheumatoid arthritis and related disorders, asthma, cancer, cardiovascular diseases, and peptic ulcer disease[4].

IDEAL PULSATILE DRUG DELIVERY SYSTEM:

Pulsatile drug delivery system is defined as the rapid and transient release of certain amount of drug molecules within a short time period immediately after a predetermined off-release period, i.e., lag time. Pulsatile drug delivery aims to release drug on programmed pattern i.e. at appropriate time and at appropriate site of action. A single dosage form provides an initial dose of drug followed by one release free interval, after which second dose of drug is released, which is followed by additional release-free interval and pulse of drug release. The pulsatile effect, i.e., the release of drug as a "pulse" after a lag time has to be designed in such a way that a complete and rapid drug release should follow the lag time may not always be desirable[5, 6].

PULSATILE SYSTEM - TO INCREASE THERAPEUTIC EFFICACY OF DRUG:

In recent years considerable attention has been focused on the development of pulsatile drug delivery system. Delivery system with pulsatile release pattern has gained most popular form of controlled drug delivery system because conventional systems with a continuous release are not ideal. Oral controlled drug delivery systems are generally used due to convenient dosage form & it also releases drug in constant or variable rates. In these system drug release generally occurs within therapeutic window for prolong period of time. Hence these systems show sustained release of drug from dosage form[7, 8].

NECESSITY OF PULSATILE DRUG DELIVERY SYSTEMS

There are many conditions and diseases where sustained release formulations do not show good efficacy. In such cases Pulsatile DDS is applicable.

1. First pass metabolism:
Some drugs, such as beta blockers, and salicylamide, 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 method of delivery would result in reduced oral bioavailability[9].

2. Biological tolerance:
Drug plasma profiles are often accompanied by a decline in the pharmacotherapeutic effect of the drug, e.g., biological tolerance of transdermal nitroglycerin, salbutamol sulphate.

3. Special chronopharmacological needs:
Circadian rhythms in certain physiological functions are well established. It has been recognized that many symptoms and onset of disease occur during specific time periods of the 24 hour day, e.g., asthma and angina pectoris attacks are most frequently in the morning hours.

4. Local therapeutic need:
For the treatment of local disorders such as inflammatory bowel disease, inflammation with no loss due to absorption in the small intestine is highly desirable to achieve the therapeutic effect and to minimize side effects.

5. Gastric irritation or drug instability in gastric fluid:
Protection from gastric environment is essential for the drugs that undergo degradation in gastric acidic medium (e.g.: peptide drugs), irritate the gastric mucosa (NSAIDS) or induce nausea and vomiting [10].

Table 1: Marketed technologies of pulsatile drug delivery[11-15].

Technology	Mechanism	Proprietary Name and dosage form	API	Disease
OROS*	Osmotic mechanism	Covera-H5*; XL tablet	Verapamil HCL	Hypertension
Three dimensional printing*	Externally regulated system	Their Form*	Diclofenac sodium	Inflammation

DIFFUCAPS*	Multiparticulate system	Innopran*; XL tablets	Verapamil HCL, Propranol HCL	Hypertension
PulsincapTM	Rupturable system	PulsincapTM	Dofetilide	Hypertension

CLASSIFICATION OF PULSATILE DRUG DELIVERY SYSTEMS:

VARIOUS APPROACHES OF PULSATILE DRUG:

Pulsatile drug delivery system can be broadly classified into three classes;

I. Time controlled pulsatile drug delivery

II. Stimuli induced pulsatile drug delivery

III. Externally regulated pulsatile drug delivery

TIME CONTROLLED PULSATILE DRUG DELIVERY

SINGLE UNIT PULSATILE SYSTEMS:

1. CAPSULE BASED SYSTEMS:

Single-unit systems are mostly developed in capsule form. The lag time is controlled by a plug, which gets pushed away by swelling or erosion, and the drug is released as a "Pulse" from the insoluble capsule body[16.]

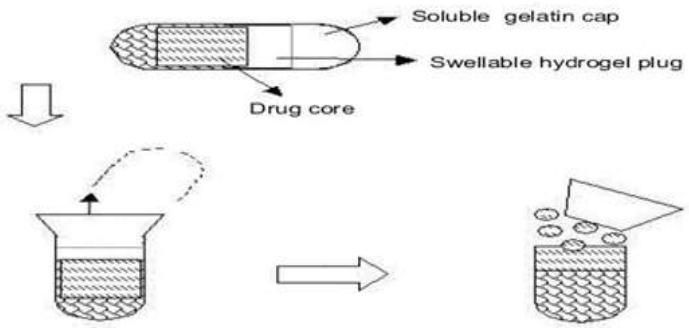

Fig 1: Design of Pulsincap system

The lag time can be controlled by manipulating the dimension and the position of the plug[17, 18]

Polymers used for designing of the hydrogel plug

1) Insoluble but permeable and swellable polymers (e.g., polyme-thacrylates)

2) Erodible compressed polymers (e.g., hydroxypropylmethyl cellulose, polyvinyl alcohol, Polyethylene oxide)

3) Congealed melted polymers (e.g., saturated polyglycolated glycerides, glyceryl monooleate)

4) Enzymatically controlled erodible polymer (e.g., pectin).

The preparation and *in vitro* release of tetramethylpyrazine phosphate pulsincap capsule has been reported.

It was prepared by sealing the drug tablet and fillers inside an impermeable capsule body with erodible plug. To meet the chronotherapeutic requirements, a suitable lag time can be achieved by adjusting the content of gel-forming polymer (HPMC) and the erodible plug weight [17-19].

2. CAPSULAR SYSTEM BASED ON OSMOSIS:

a. 'PORT' System

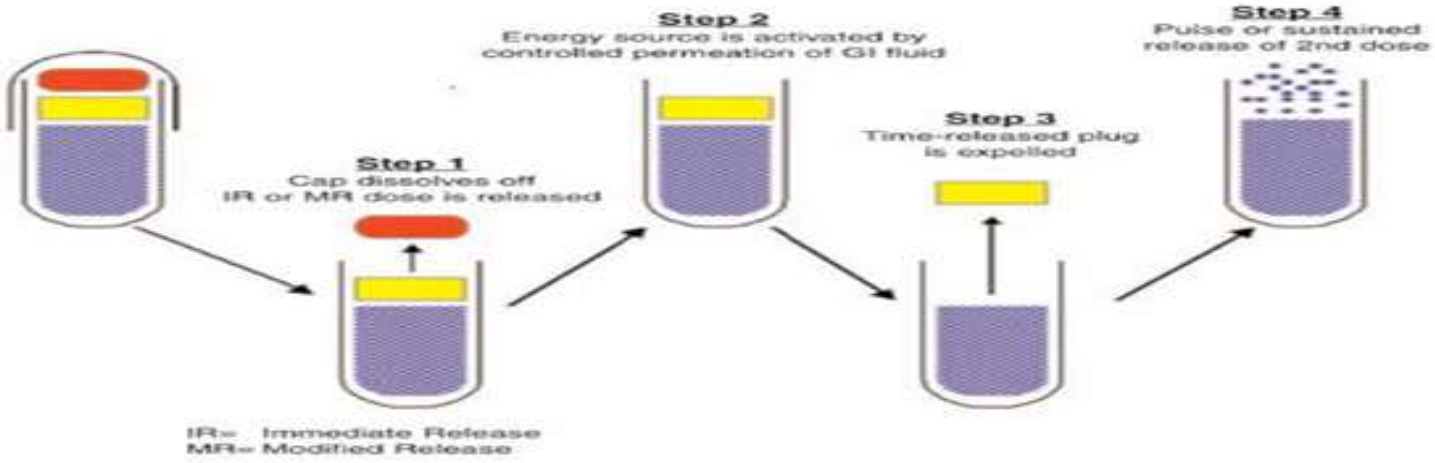

Fig 2: Drug release mechanism from PORT system

The Port system fig. was developed by Therapeutic system research laboratory Ann Arbor, Michigan, USA, and consists of a capsule coated with a semipermeable membrane. Inside the capsule was an insoluble plug consisting of osmotically active agent and the drug formulation. When this capsule came in contact with the dissolution fluid, the semipermeable membrane allowed the entry of water, which caused the pressure to develop and the insoluble plug expelled after a lag time. Such a system was utilized to deliver methylphenidate used in the treatment of attention deficit hyperactivity disorder as the pulsatile port system.

This system avoided second time dosing, which was beneficial for school children during daytime.

b. System based on expandable orifice[20]

To deliver the drug in liquid form, an osmotically driven capsular system was developed in which the liquid drug is absorbed into highly porous particles, which release the drug through an orifice of a semipermeable capsule supported by an expanding osmotic layer after the barrier layer is dissolved.

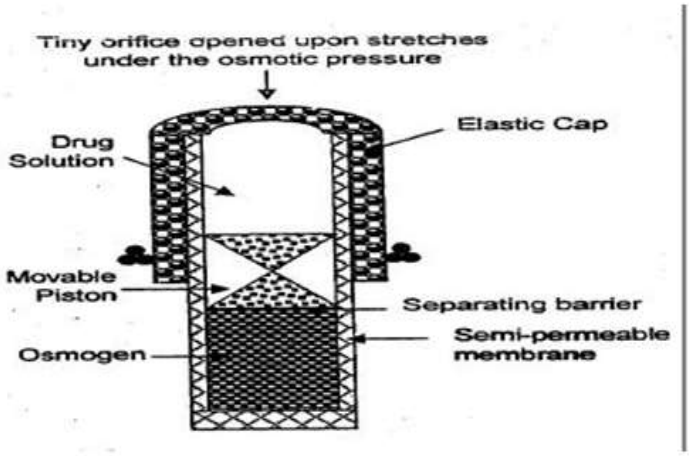

Figure 3: System based on expandable orifice

The orifice is small enough so that when the elastic wall relaxes, the flow of the drug through the orifice essentially stops, but when the elastic wall is distended beyond threshold value, the orifice expands sufficiently to allow drug release at a required rate. E.g. Elastomers, such as styrene-butadiene copolymer have been suggested.

c. Delivery by series of stops:

This system is described for implantable capsules. The capsule contains a drug and a water absorptive osmotic engine that are placed in compartments separated by a movable partition. The pulsatile delivery is achieved by a series of stops along the inner wall of the capsule. These stops obstruct the movement of the partition but are overcome in succession as the osmotic pressure rises above a threshold level[21].

d. Pulsatile delivery by solubility modulation:

Such systems contain a solubility modulator for pulsed delivery of variety of drugs. The system was especially developed for delivery of salbutamol sulphate[22, 23].The compositions contain the drug (salbutamol sulphate) and a modulating agent (sodium chloride). The amount of NaCl was such that it was less than the amount needed to maintain saturation in a fluid that enters the osmotic device. The pulsed delivery is based on drug solubility. Salbutamol has solubility of 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.

3. PULSATILE SYSTEM WITH ERODIBLE OR SOLUBLE BARRIER COATINGS:

Most of the pulsatile drug delivery systems are reservoir devices coated with a barrier layer. This barrier erodes or dissolves after a specific lag period, and the drug is subsequently released rapidly from reservoir core. The lag time depends on the thickness of the coating layer[22, 23].

a. The chronotropic system:

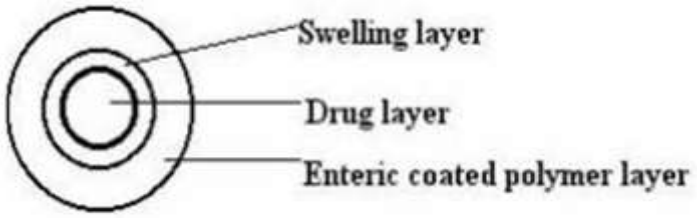

Figure 4: The chronotropic system

The Chronotropic® system consists of a drug-containing core coated by hydrophilic swellable hydroxypropylmethyl cellulose (HPMC), which is responsible for a lag phase in the onset of release [24, 25]. In addition, through the application of an outer gastric-resistant enteric film, the variability in gastric emptying time can be overcome, and a colon-specific release can be obtained, relying on the relative reproducibility of small intestinal transit time. The lag time is controlled by the thickness and the viscosity grades of HPMC. Both in-vitro and in-vivo lag times correlate well with the applied amount of the hydrophilic retarding polymer. The system is suitable for both tablets and capsules.

b. 'TIME CLOCK' System:

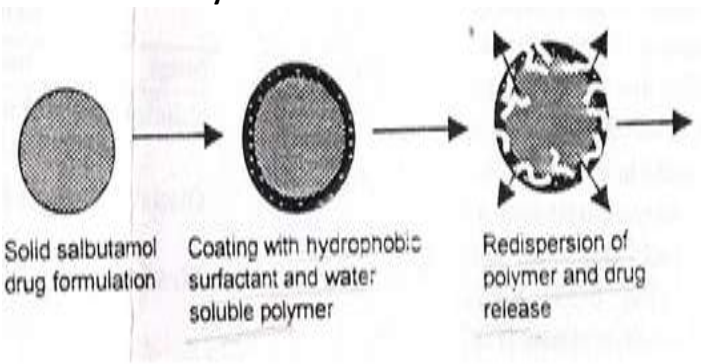

Figure 5: 'TIME CLOCK' System

The lag time could be controlled by varying the thickness of the film. After the lag time, i.e., the time required for rehydration, the core immediately releases the drug. 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.

c. Compressed Tablets:

Compression coating can involve direct compression of both the core and the coat, obviating

needs for separate coating process and use of coating solutions. The outer tablet of the compression-coated tablet provides the initial dose, rapidly disintegrating in the stomach and the inner layer is formulated with components that are insoluble in gastric media but are released in the intestinal environment. Materials such as hydrophilic cellulose derivates can be used. Compression is easy on laboratory scale. The major drawbacks of the technique are that relatively large amounts of coating materials are needed and it is difficult to position the cores correctly[26].

Press-coated pulsatile drug delivery systems:

1. Press-coated pulsatile drug delivery systems can be used to protect hygroscopic, light-sensitive, oxygenlabile or acid-labile drugs.
2. Press-coated pulsatile drug delivery systems are relatively simple and cheap.
3. These systems can involve direct compression of both the core and the coat.
4. Materials Such as hydrophobic, hydrophilic can be used in press-coated pulsatile drug delivery system.
5. Press-coated pulsatile drug delivery systems involve compression which is easy on laboratory scale.
6. Press-coated pulsatile formulations release drug after "lag-time".
7. Press-coated pulsatile drug delivery formulations can be used to separate incompatible drugs from each other or to achieve sustained release.

d. Multilayered Tablets:

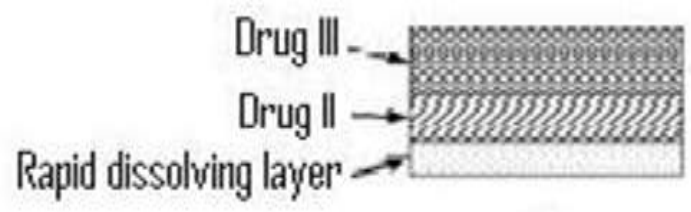

Figure 6: Multilayered Tablet

A release pattern with two pulses was obtained from a three layered tablet containing two drug containing layers separated by a drug-free gellable polymeric barrier layer[27-29].

4. Pulsatile system with rupturable coating:

These systems depend on the disintegration of the coating for the release of drug. The pressure necessary for the rupture of the coating can be achieved by the effervescent excipients, swelling agents, or osmotic pressure. An effervescent mixture of citric acid and sodium bicarbonate was incorporated in a tablet core coated with ethyl cellulose. The carbon dioxide developed after penetration of water into the core resulted in a pulsatile release of drug after rupture of the coating. The release may depend on the mechanical properties of the coating layer[30].

a) Pulsatile system based on rupturable coating:

E.g. Time –controlled Explosion system (TCES):

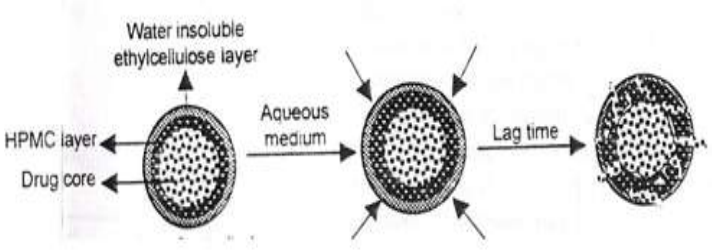

Figure 7: Time –controlled Explosion system (TCES)

This is a multiparticulate system in which drug is coated on non-pareil sugar seeds followed by a swellable layer and an insoluble top layer. The swelling agents used include Superdisintegrants like sodium carboxymethyl cellulose, sodium starch glycollate, L hydroxypropyl cellulose. Polymers like polyvinyl acetate, polyacrylic acid, polyethylene glycol, etc.

b) Osmotic based rupturable coating system:

This system is based on a combination of osmotic and swelling effects. The core containing the drug, a low bulk density solid and/or liquid lipid material (e.g.: mineral oil) and a disintegrant was prepared. This core was then coated with cellulose acetate. Upon immersion in aqueous medium, water penetrates the core displacing lipid material. After the depletion of lipid material, internal pressure increases until a critical stress is reached, which results in rupture of coating.

c) Pulsatile delivery by change in membrane permeability:

The permeability and water uptake of acrylic polymers with quaternary ammonium groups can be influenced by the presence of different counter-ions in the medium. 48 Several delivery systems based on this ion exchange have been developed. Eudragit RS 30D is reported to be a polymer of choice for this purpose. It typically contains positively polarized quaternary ammonium group in the polymer side chain, which is always accompanied by negative hydrochloride counter-ions. The ammonium group being hydrophilic facilitates the interaction of polymer with water, thereby changing its permeability and allowing water to permeate the active core in a controlled manner. This property is essential to achieve a precisely defined lag time[31].

STIMULI-INDUCED PULSATILE RELEASE:

1. TEMPERATURE-INDUCED PULSATILE RELEASE:

Thermoresponsive hydrogels have been investigated as possible drug delivery carriers for stimuli responsive drug delivery systems[32-34]. PIPAAm cross-linked gels have shown thermoresponsive, discontinuous swelling / deswelling phases: swelling, for example, at temperatures below 32˚C, while shrinking above this temperature.

Thermoresponsive polymeric micelle systems As Kataoka et al. comprehensively reviewed, the properties and biological interests of polymeric micelles make them a most noteworthy candidate as drug carrier for the treatment of cancer. The polymeric micelle is composed of amphiphilic block copolymers exhibiting a hydrophobic core with a hydrophilic corona. The application of a temperature gradient induced an on–off drug release regulation from PIPAAm PBMA micelles between 4 and 37˚C.

2. CHEMICAL STIMULI-INDUCED PULSATILE RELEASE:

a) Glucose-responsive insulin release devices

A decrease in or the absence of insulin secretion from pancreatic islets is the cause of diabetes mellitus. Diabetes mellitus patients suffer long term from a gradual decline in the efficiency of various organs, such as the occasional loss of eyesight. Several systems have already been developed which are able to respond to glucose concentration changes. Glucose oxidase (GOD) catalyzes glucose oxidation. Utilizing this reaction, Ishihara et al. prepared two types of gel membrane systems to regulate insulin permeability. They prepared and nicotinamide-immobilized gel membranes, separately. Inflammation-induced pulsatile release

When Human beings receive physical or chemical stress, such as injury, broken bones, etc; inflammation reactions take place at the injured sites.

At the inflammatory sites, inflammation-responsive phagocytic cells, such as macrophages and polymorph nuclear cell play a role in the healing process of the injury. During inflammation, hydroxyl radicals (OH) are produced from these inflammation-responsive cells. Yui and co-workers [33, 34] used hyaluronic acid (HA), a linear mucopolysaccharide composed of repeating disaccharide subunits of N-acetyl-D-glucosamine and D-guluronic acid. In the body, HA is mainly degraded either by a specific enzyme, hyaluronidas, or hydroxyl radicals. Degradation of HA via the hyaluronidase is very low in a normal state of health. Degradation via hydroxyl radicals however, is usually dominant and rapid when HA is injected at inflammatory sites. Thus, Yui and co-workers prepared cross-linked HA with ethylene glycol diglycidylether or polyglycerol polyglycidyl ether. These HA gels degraded only when the hydroxyl radicals were generated through the Fenton reaction between Fe+2 ions and hydrogen peroxide in vitro. Thus, a surface erosion type of degradation was achieved. When microspheres were incorporated in the HA hydrogels as a model drug, these microspheres were released only when hydroxyl radicals induced HA gel degradation. The microsphere release was regulated by the surface erosion type of degradation.

b) 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/de-swelling characteristics.

Miyata and co-workers focused on the introduction of stimuli-responsive cross-linking structures into hydrogels. Special attention was given to antigen antibody complex formation as the cross-linking units in the gel, because specific antigen recognition of an antibody can provide the basis for a new device fabrication.

c) Electric stimuli-responsive pulsatile release

The combination of developments in several technologies, such as microelectronics and micromachining, as well as the potential need for chronotherapy, have currently assisted the development of electronically assisted drug delivery technologies. These technologies include iontophoresis, infusion pumps, and sonophoresis. Several approaches have also been presented in the literature describing the preparation of electric stimuli-responsive drug delivery systems using hydrogels. Kishi et al[35] developed an electric stimuli induced drug release system using the electrically stimulated swelling /de-swelling characteristics of polyelectrolyte hydrogels. They utilized a chemo-mechanical system, which contained a drug model within the polyelectrolyte gel structure. These gels exhibited reversible swelling / shrinking behavior in response to on–off switching of an electric stimulus. Thus, drug molecules within the polyelectrolyte gels might be squeezed out from the electric stimuli-induced gel contraction along with the solvent flow. To realize this mechanism, poly (sodium acrylate) microparticulate gels containing pilocarpine as a model drug were prepared.

ADVANCED TECHNOLOGY:

Currently pharmaceutical company focused on developing and commercializing pulsatile drug products that fulfill unmet medical needs in the treatment of various diseases. For several diseases (e.g. bronchial asthma, hypertension, rheumatic disease and myocardial infarction) as well for control of body functions (blood pressure, levels of many hormones e.g. aldosterone, rennin, and Cortisol) influenced by circadian rhythms, delayed or pulsatile drug release could be an optimal approach. Recently develop various technologies are ACCU-BREAK™, AQUALON, CODAS®, PRODAS®, SODAS®, MINITABS®, DIFFUCAPS®, OROS® etc.

CURRENT SITUATION AND FUTURE SCOPE:

Now a day's pulsatile drug delivery is gaining popularity. The prime advantage in this drug delivery is that drug is released when necessity comes. As a result chance of development of drug resistance which is seen in conventional and sustained release formulations can be reduced. Furthermore, some anticancer drugs are very toxic. These drugs give hazardous problems in conventional and sustained release therapies. Now many FDA approved chronotherapeutic drugs are available in the market. This therapy is mainly applicable where sustained action is not required and drugs are toxic. Key point of development of this formulation is to find out circadian rhythm i.e. suitable indicator which will trigger the release of drug from the device. Another point is absence of suitable rhythmic biomaterial which should be biodegradable, biocompatible and reversibly responsive to specific biomarkers in rhythmic manner. Regulatory is another big question. In preapproval phase it is sometimes difficult to show chronotherapeutic advantage in clinical settings. In post approval phase causal recreational drug abuse along with on a much larger scale, by the criminal diversion of these modified formulations for profit have arisen problems. The FDA has now heavily relied on the development and implementation of risk management programs as a strategy to allow an approval of a drug to go forward while exercising some restrictions. Many researches are going on the pulsatile drug delivery to discover circadian rhythm with suitable device in the world. In future this delivery will be a leading way to deliver therapeutic agents due to its some unique characters like low chance of dose dumping, patient compliance and the above factors[36].

CONCLUSION:

Research in chronopharmacology has demonstrated the importance of biological rhythms in drug therapy and this has led to a new approach to the development of drug delivery systems. Optimal clinical outcome cannot be achieved if drug plasma concentrations are constant. Circadian disorders such as hypertension, osteoarthritis, Asthma etc., which require chronopharmacotherapy. PDDS can effectively tackle this problem as it is modulated according to body's circadian clock giving release of drug after a specified time lag. Circadian rhythm of the body is an important concept for understanding the optimum need of drug in the body. There is a constant need for new delivery systems that can provide increased therapeutic benefits to the patients.

Pulsatile drug delivery is one such system that, by delivering drug at the right time, right place and 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 enhances the patient compliance, optimum drug delivery to the target site and minimizes the undesired effects. The approaches in this article represent attempts conducted over the past decade to achieve pulsatile release. It should be pointed that these drug delivery systems are still in the early developmental stage and much research will have to be conducted for such systems become practical clinical alternatives.

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