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Review Article

Newer insights into pulsatile drug delivery systems

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ABSTRACT

In present time advancement are going on to develop Modified dosage form i.e. sustain release, controlled release and extended release dosage formulation to improve way of therapeutic treatment, to improve patient convenience and compliance toward drug therapy. Through the recent studies, it was found that number of normal body function and disease condition show chronobiological behavior. It was found that occurrence of diseases like asthma, peptic ulcers, cardiovascular ailments, arthritis and attention deficit syndrome in children and hypercholesterolemia shows circadian rhythm dependency. This leads to development of intelligent drug delivery system called 'Pulsatile drug delivery system (PDDS).This system are designated to deliver drug in Pulse after predetermined lag time to match circadian rhythm of particular disease. This concept has several advantages, notably maximum therapeutic benefit, minimum harm, improved patient convenience and compliance. Pharmacists must realize the need to develop and dispense such medications having potential therapeutic benefit. The current article focuses on reasons for development of pulsatile drug delivery system, diseases requiring PDDS, Necessity of PDDS, classification, evaluations, advantages, limitation, future aspects and PDDS product currently available in the market.

Key Words: Chronotherapy, Chronopharmaceutics, Pulsatile Drug Delivery System (PDDS), circadian rhythm

INTRODUCTION

Since the time of immemorial centuries, oral route of drug administration has been one of the most convenient, more patient compliance for this route of delivery for most therapeutic agents. The system for the release of various drugs have been designed in such a way that focused on constant, variable; sustain drug release and/or targeting the therapeutic agent to a specific site/tissue/organ. However, recently there are some specific conditions for which conventional release pattern is not suitable and it requires some sort of timed release of therapeutic agents at specific site. So there is need to develop a system which is capable of releasing drug after predetermined time delay or lag time and maintain constant drug release for specified time. These drug deliveries are generally known as pulsatile drug delivery systems (PDDS), sigmoidal release systems (Fig. 1) or time-controlled systems. This system is characterized by no drug release for certain time interval (known as lag time) followed rapid burst or sustained release of drug. [1-10] Different terminologies used for describing this type of delivery of medications at specified time are enlisted and defined figure 1.

Chronotherapy: [11, 12]
Co-ordination of biological rhythms and medical treatment is called as chronotherapy.

Chronotherapeutics: [11, 12]
Chronotherapeutics is a discipline concerned with the delivery of drugs according to inherent activities of a disease over a certain period of time. It is becoming increasingly more evident that the specific time of drug administration to the patients may be even more significant. The tradition of prescribing medication at evenly spaced time intervals throughout the day, in an attempt to maintain constant drug levels throughout a 24 hr period, may be indicating that the some medications may work better if their administration is coordinated with day-night patterns and biological rhythms.

Chronobiology: [12, 13]
Chronobiology is the science concerned with the biological mechanism of the diseases according to

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a time structure. "Chrono" relates to time and "biology" relates to the science of life.

Chronopharmacology: [12, 13]
Chronopharmacology is the science concerned with the variations in the pharmacological actions of various drugs over a period of time of the day.

Chronopharmacokinetics: [12, 14]
Chronopharmacokinetics involves study of time related changes in drug absorption, distribution, metabolism and excretion. Pharmacokinetic parameters, which are influenced by different physiological functions displaying circadian rhythm. Circadian changes in gastric acid secretion, gastrointestinal motility, gastrointestinal blood flow, drug protein binding, liver enzyme activity, renal blood flow and urinary pH can play role in time dependent variation of drug plasma concentrations.

BIOLOGICAL RHYTHMS [15, 16]

Ultradian Rhythms: Oscillations of shorter duration are termed ultradian rhythms (more than one cycle per 24 hr). E.g. 90 minutes sleep cycle.

Infradian Rhythms: Oscillations that are longer than 24 hr are termed as infradian rhythms (less than one cycle per 24 hr). e.g. Monthly menstruation.

Circadian rhythms: Circadian rhythms are self-sustaining, endogenous oscillations that occur with a periodicity of about 24 hr. Interestingly, the term circadian is derived from the Latin circa which pertains to "about" and dies which can be outlined as "a day". Normally, circadian rhythms are the internal biologic clocks related to the sleep-wake cycle. Our circadian rhythm is affected by our genetic makeup and there by affects our bodies' function throughout day and night (24 hr period). Circadian rhythm regulates many body functions in humans like metabolism, physiology, behavior, sleep pattern, hormone production. There are number of conditions in which advantage could be taken by timing and adjusting the administration of drugs according to the circadian rhythm of the disease as depicted in Figure 2.

NEED OF PULSATILE DRUG DELIVERY [15, 17-18]

Below are the basic advantages of pulsatile drug delivery over the conventional drug delivery.

First pass metabolism: Some drugs, such as salicylamide and beta blockers, undergo extensive first pass metabolism and requires higher amount of free drug achieved by fast release to saturate metabolizing enzymes in order to minimize pre-systemic metabolism. So in order to avoid first pass metabolism, it is advisable to use pulsatile drug delivery systems over conventional or sustained drug delivery dosage form.

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 nitroglycerin.

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, arthritis are most frequently in the morning hours.

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

Gastric irritation or drug instability in gastric fluid: For drugs with chemical instability in gastric fluid and gastric irritation or, the use of a sustained release preparation may exacerbate gastric irritation and chemical instability in gastric fluid.

Drug absorption differences in various gastrointestinal segments: Usually drug absorption is moderately slow in the stomach, rapid in the small intestine, and sharply declining in the large intestine. Compensation for changing absorption characteristics in the gastrointestinal tract may be important for some drugs. For example, it is rational for a delivery system to pump out the drug much faster when the system reaches the distal segment of the intestine and to avoid the excretion of the drug in the feces.

To Design multiple daily dosage regimen: It could accomplish multiple daily dosing regimens for those drugs that fail to be candidate for prolonged-release formulations, e.g. because of a strong first-pass effect or pharmacological tolerance. Recently, multi-pulse delivery of antibiotics has also been described as a means of limiting the development of resistant bacterial strains thus possibly improving the outcome of infectious disease therapy

Minimize drug-drug interaction: Delayed-release dosage forms have been proposed to prevent the occurrence of potential drug–drug interactions without altering the administration schedule of

combined medications, which could negatively affect the patient compliance.

ADVANTAGES OF PULSATILE DRUG DELIVERY SYSTEM: [19, 20]

- Extended daytime or nighttime activity
- Reduced side effects
- Reduced dosage frequency
- Reduction in dose size
- Improved patient compliance
- Lower daily cost to patient due to fewer dosage units are required by the patient in therapy.
- Drug adapts to suit circadian rhythms of body functions or diseases.
- Drug targeting to specific site like colon.
- Protection of mucosa from irritating drugs.
- Drug loss is prevented by extensive first pass metabolism.
- Patient comfort and compliance: Oral drug delivery is the most common and convenient for patients, and a reduction in dosing frequency enhances compliance.

LIMITATIONS OF PULSATILE DRUG DELIVERY SYSTEM: [21]

Pulsatile drug delivery systems have certain limitation, so in many cases these drug delivery system is fails,

· Multiple manufacturing steps in case of Multiparticulate pulsatile drug delivery system.

· Low drug load

· Incomplete release

· In-vivo variability in single unit pulsatile drug delivery system.

DISEASES AND CHRONOTHERAPEUTICS

The major or potential benefits of chronotherapeutics have been established in the management of several of diseases. But specifically there is a lot of interest in how chronotherapy can mostly advantageous for the patients distressed from allergic rhinitis, rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, asthma, cancer, cardiovascular diseases, and peptic ulcer disease.[14] Following Table-1 illustrate the diseases influenced by chronotherapy and Table-2 disease required PDDs.

Rheumatoid Arthritis: Rheumatoid arthritis is a long-lasting inflammatory autoimmune condition. The signs and symptoms of rheumatoid arthritis are toughness, bulging and pain of joints of the body typically most unadorned in the morning. Rheumatoid arthritis shows a marked diurnal variation in its symptoms. [22, 23] A group of British volunteers self-assessed the pain and stiffness of affected finger joints every 2 to 3 h daily for several consecutive days. They also measured the circumference of the arthritic joints to gauge the amount of their swelling, and they performed grip strength tests to determine the effect of the arthritic condition on the hands. Ratings of the severity of joint pain swelling and stiffness were about 3 times higher in early morning than at bedtime. In contrast, hand strength was lower by as much as 30% in the morning than at night. This is typical of rheumatoid arthritis sufferers. [24, 25]

The symptoms of rheumatoid arthritis are always worse in the morning. The long-acting Non-Steroidal Anti-inflammatory Drugs (NSAIDs) like flubiprofen, ketoprofen and indomethacin at bedtime optimizes their therapeutic effect and diminishes or obviates their side effects. 12-hour sustained-release NSAIDs that are taken twice a day must include a night or bedtime ingestion time to safeguard satisfactory control of the noticeable morning symptoms of rheumatoid arthritis. If the arthritic condition is severe, synthetic corticosteroids are a lot of advantage. Morning once-a-day dosing of these drugs is least probable to cause side effects particularly if they are taken for a long period of time. Splitting the daily dose of medicine into several small ones for ingestion with meals and at bedtime or taking the entire daily dose at night is not recommended unless unconditionally essential. The risk of severe side effects from these medications increases when they are taken more than 8 to 9 h after the usual time of awakening, after 15:00 pm for most people. The later in the day these medicines are taken, the greater the risk of side effects. If the relief from the morning symptoms of rheumatoid arthritis sufferers is not reached by a once-day morning schedule, an increase in the morning dose is recommended. The results of one study suggest an early afternoon once-a-day treatment schedule might be beneficial for those people who fail to get significant relief from the morning pain and stiffness of rheumatoid arthritis when taking medicine in the morning. [26-28]

Osteoarthritis: The diurnal rhythm of pain and stiffness in osteoarthritis differs from that of rheumatoid arthritis. Osteoarthritis is a degenerative disease of the joints and is the commonest of all joint diseases, affecting nearly everyone at least to some degree by age 70. The load bearing joints of the hip, knee, back, toes and fingers are mostly exaggerated. The pain of osteoarthritis victims is classically less intense in the morning than in the afternoon or evening. This is exemplified by the findings of a Canadian study of 20 persons distressed with osteoarthritis of the knee. Accomplices did pain self-ratings 10 times daily for 7 consecutive days. For the group as a

whole, pain intensity was rated about 40 percent higher on average between 20:00 pm and midnight than between 06:00 and 10:00 am. However, the exact nature of the 24 h pattern of pain differed from person to person. In 40 percent, pain was highest between 14:00 and 20:00 pm, and in 25%, it was peak between 20:00 pm and midnight. In 15 %, it peaked at two different times of the day, and in 20 %, the level of pain showed no day-night variation whatever. Interestingly, 40 % of the people exhibited weekly rhythms in pain intensity, although the exact day of the week it was worse varied. In some, it was more intense at the end of the week and in others the beginning. In summary, the day-night cycle of pain in osteoarthritis varies from one individual to another. Some experience worse pain in the morning and others at night. Some experiences two peaks i.e. in the morning and evening, while still others experience pain of equal intensity throughout the 24 h. The successful treatment of osteoarthritis requires that medicines be taken at the right time relative to the day-night pattern of pain in each person.

The chronological pattern of pain and arduousness in osteoarthritis sufferers differs between persons. Thus, an adapted chronotherapy of NSAIDs is necessary. The chronotherapy of osteoarthritis involves the administration of once-a-day forms of ketoprofen, indomethacin and other such medicines in relation to the time of day pain is worse. If pain is worse at night or early in afternoon, an evening once a day NSAIDs schedule is suggested. If pain is worse in the afternoon or night, a once-a-day morning or noontime treatment schedule is best, providing the amount of side effects produced by the morning one, in particular, is minimal. [29, 30]

Ankylosing Spondylitis: Ankylosing spondylitis is characterized by bulge and uneasiness of the joints of the back. In its occurrence it is a congenital disorder that is more common in men than women. One investigator used questionnaires to study daily cycles in the back symptoms of 39 people suffering from this disease. Overall, back stiffness and pain were a problem throughout the 24 h, but pain intensity was rated 2 to 3 times higher and stiffness about 8 times greater between 06:00 and 09:00 am than between noon and 15:00 pm when each was least worrisome. The symptoms also exhibited a second less noticeable peak between 19:00 and 21:00 pm. The findings of a French study of 26 people suffering from this medical condition were identical. Ratings of the intensity of back arduousness and pain were higher in the morning and evening than in the afternoon. Marked seasonal variation in ankylosing spondylitis was also noticeable. The onset of backache and stiffness was 12 times more frequent in winter than summer. Moreover, reoccurrence of back problems occurs 2 to 3 times more often in winter than summer. [31, 32]

CLASSIFICATION OF PULSATILE DRUG DELIVERY SYSTEMS [35]

Time controlled pulsatile drug delivery: These time-controlled systems can be classified as single unit (e.g., tablet or capsule) or multiple unit systems.

Single Unit Systems

Capsule based systems: Single-unit systems are generally developed in capsule form. The lag time is mainly controlled by a plug, which gets pushed away from capsule body by swelling or erosion, and the drug is released as a "Beat" from the unsolvable capsule body (Figure 4). [36] The lag time can be controlled by influencing the dimension and the position of the plug. [37, 38]

Polymers used for designing and development of the hydrogel plug includes 1) Insoluble although permeable and swellable polymers (e.g., polymethacrylates) 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). [37, 38]

The preparation and invitro 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 concentration of gel-forming polymer (HPMC) and the erodible plug weight. [39-41]

Capsular system based on Osmosis

PORT' System [42]: The Port system Figure 5 was developed by Therapeutic system research laboratory Ann Arbor, Michigan, USA, and consists of a capsule coated with a semipermeable membrane. Inside the capsule there was an unsolvable plug consisting of osmotically active agent and the drug formulation. [42] Upon contact with the dissolution liquid, the semipermeable membrane of capsule allows the entry of water, which creates the pressure inside the capsule which led to discharge of the insoluble plug after a lag time. Such a system was exploited 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.

System based on expandable orifice [43-45]: 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 reinforced by an expanding osmotic layer after the barrier layer is dissolved (Figure 6). [43] 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 expanded beyond threshold value, the orifice expands sufficiently to allow drug release at a required rate. E.g. Elastomers, such as styrenebutadiene copolymer have been suggested. [44, 45]

Delivery by series of stops [46]: This system is described for implantable capsules. The capsule contains a drug and a water absorptive osmotic engine that are placed in barriers separated by a movable partition. The pulsatile delivery is achieved by a series of stops along the inner wall of the capsule. These stops block the movement of the partition but are overcome in sequence as the osmotic pressure rises above a threshold level. [46]

Pulsatile delivery by solubility modulation [47-49]: Such systems contain a solubility modulator for pulsed delivery of variety of drugs. The system was especially developed for delivery of salbutamol sulphate. 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.

Pulsatile system with Erodible or soluble barrier coatings [51-53]: Most of the pulsatile drug delivery systems are reservoir devices coated with a barrier layer. This barrier corrodes or dissolves after a specific lag period, and the drug is afterward released rapidly from reservoir core. The lag time depends on the thickness of the coating layer.

The chronotropic system: [50-55]: 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 (Figure 7).[52] In addition, through the application of an outer gastric-resistant enteric film, the variability in gastric emptying time can be flabbergasted, and a colon-specific release can be obtained, relying on the relative reproducibility of small intestinal transit time.[53] The lag time is controlled by the thickness and the viscosity grades of HPMC.[54] Both *In-Vitro* and *In- Vivo* lag times correlate well with the applied amount of the hydrophilic retardin polymer. The system is suitable for both tablets and capsules. [55]

'TIME CLOCK' System [50-55] : The lag time could be controlled by varying the fatness of the film. After the lag time, i.e., the time required for rehydration, the core immediately releases the drug (Figure 8). 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.

Compressed Tablets: [56-58] Compression coating can involve direct compression of both the core and the coat, avoiding 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. [56] Materials such as hydrophilic cellulose derivate 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. [56] 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 relese 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.

Multilayered Tablets: [57-59] 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 (Figure 9). [57-59]

Multiparticulates / Multiple unit systems

Pulsatile system with rupturable coating [60-63] 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 (Figure 10). [60] E.g. 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 glycolate, L-hydroxypropyl cellulose. Polymers like polyvinyl acetate, polyacrylic acid, polyethylene glycol, etc. [61-63]

Instead, an effervescent system comprising a mixture of tartaric acid and sodium bicarbonate may also be used. Upon ingress of water, the swellable layer expands, resulting in rupture of film with subsequent rapid drug release. The release is independent of environmental factors like pH and drug solubility. The lag time can be varied by varying coating thickness or adding high amounts of lipophilic plasticizer in the outermost layer. A rapid release after the lag phase was achieved with increased concentration of osmotic agent In vivo studies of time-controlled explosion system (TCES) with an in-vitro lag time of three hours showed appearance of drug in blood after 3 hrs, and maximum blood levels after 5 hrs. [63]

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. [64] The osmotic agents dissolve in the water causing the pellets to swell, thereby regulating the rate of drug diffusion. The effect of each pellet population releasing its drug content sequentially provides a series of pulses of drug from a single dosage form. The coating thickness can be varied amongst the pellets.

Pulsatile delivery by change in membrane permeability [65, 66] 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. [65] 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. The cores were prepared using theophylline as model drug and sodium acetate. These pellets were coated using Eudragit RS30D (10% to 40% weight gain) in four different layer thicknesses. A correlation between film thickness and lag time was observed. It was found that even a small amount of sodium acetate in the pellet core had a dramatic effect on the drug permeability of the Eudragit film. After the lag time, interaction between the acetate and polymer increases the permeability of the coating so considerably that the entire active dose is enlightened within a few minutes. The lag time increases with increasing thickness of the coat, but the release of the drug was found to be independent of this thickness and depended on the amount of salt present in the system. [66]

Stimuli induced pulsatile drug delivery

Temperature-induced pulsatile release: [67-70] Thermo responsive hydrogels have been explored as possible drug delivery carriers for stimuli responsive drug delivery systems. [67-69] Poly (Nisopropylacrylamide) (PIPAAm) cross-linked gels have shown thermo responsive, discontinuous swelling / deswelling phases: swelling, for example, at temperatures below 328°C, while shrinking above this temperature. Thermo responsive polymeric micelle systems as Kataoka et al. [70] 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 378 °C.

Chemical stimuli induced pulsatile systems

Glucose-responsive insulin release devices [71-73] 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. [71] 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 cells 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 [72, 73] 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, hyaluronidase, 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 [72, 73] prepared cross-linked HA with ethyleneglycol diglycidylether or polyglycerol polyglycidylether. 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.

Drug release from intelligent gels responding to antibody concentration [74, 75] 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. Miyata and coworkers 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.

Electric stimuli-responsive pulsatile release [76-78] The combination of developments in several technologies, such as microelectronics and micromaching, 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. [76] Several approaches have also been presented in the literature describing the preparation of electric stimuli-responsive drug delivery systems using hydrogels. Kishi et al. [77] developed an electric stimuli induced drug release system using the electrically stimulated swelling /deswelling characteristics of polyelectrolyte hydrogels. They utilized a chemomechanical 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. [78]

Externally Regulated Pulsatile System

Micro Electro Mechanical Systems (MEMS) [79, 80] A micro fabricated device has the ability to store and release multiple chemical substances on demand by a mechanism devoid of moving its parts. The digital capabilities of MEMS may allow greater temporal control over drug release compared to traditional polymer-based systems. Another development in MEMS technology is the microchip. The microchip consists of an array of reservoirs that extend through an electrolyte-impermeable substrate. The prototype microchip is made of silicon and contains a number of drug reservoirs; each reservoir is sealed at one end by a thin gold membrane of material that serves as an anode in an electrochemical reaction and dissolves when an electric potential is applied to it in an electrolyte solution. The reservoirs are filled with any combination of drug or drug mixtures in any form (i.e. solid, liquid or gel). When release is desired, an electric potential is applied between an anode membrane and a cathode, the gold membrane anode dissolves within 10-20 seconds and allows the drug in the reservoir to be released. This electric potential causes oxidation of the anode material to form a soluble complex with the

electrolytes which then dissolves allowing release of the drug. Complex release patterns (such as simultaneous constant and pulsatile release) can be achieved from the microchips. Microchip has the ability to control both release time and release rate.

Magnetically stimulated system [81] Use of an oscillating magnetic to regulate the drug delivery from a polymer matrix was one of the first methodologies investigated to develop an externally controlled drug delivery system. Magnetic carriers receive a response to a magnetic field from incorporated materials such as magnetite, iron, nickel, cobalt, etc. For biomedical applications, magnetic carriers must be water-based, biocompatible, non-toxic and non-immunogenic. Basically the mechanistic approach behind the strategy is based on the slowing down the movement of oral drugs in the gastrointestinal system through magnetic attraction. This is possible by filling an additional magnetic component into capsules or tablets. The speed of travel through the stomach and intestines can then be slowed down at specific positions by an external magnet, thus changing the timing and or extent of drug absorption into stomach or intestines

Ultrasonically stimulated system [82] Ultrasound is mostly used as an enhancer for the improvement of drug permeation through biological barriers, such as skin. The interactions of ultrasound with biological tissues are divided into two broad categories: thermal and nonthermal effects. Thermal effects are associated with the absorption of acoustic energy by the fluids or tissues. Non-thermal bio-effects are generally associated with oscillating or cavitating bubbles, but also include noncavitation effects such as radiation pressure, radiation torque, and acoustic streaming. 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.

Photo stimulated system [83] 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. Light-sensitive hydrogels have potential applications in developing optical switches, display units, and ophthalmic drug delivery devices.

Review of literature for pulsatile drug delivery system: Here, list of drugs (Table-3) were used in various pulsatile drug delivery system.

Recent advances in the pulsatile drug delivery: 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 by researchers 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 (Table-4).

OROS® technology: Chronset™ is a proprietary OROS® delivery system that reproducibly delivers a bolus drug dose in a time- or site-specific manner to the gastrointestinal tract. It is nothing but osmosis based system. The active pharmaceutical is kept in a reservoir surrounded by a semipermeable membrane laser drilled with a delivery orifice and formulated into a tablet. There are two layers in this tablet comprising of one drug layer and another osmotically active agent. Upon contact with GI fluid this osmotic agent changes its characteristic from non-dispensable to dispensable viscosity. As a result active pharmaceutical is pushed away through the channel due to pump effect of the osmotic agent. It is used generally for designing of extended release tablet. [94]

CEFORM®: It produces uniformly sized and shaped microspheres of pharmaceutical compounds. This approach is based on "melt-spinning" which means subjecting solid feedstock (i.e. biodegradable polymer/ bioactive agent combinations) to a combination of temperature, thermal gradients, mechanical forces, flow and flow rates during processing. The microspheres obtained are almost perfectly spherical, having a diameter that is typically of 150–180 mm, and allow for high drug content. The microspheres can be used in a wide variety of dosage forms including tablets, capsules, suspensions, effervescent tablets and sachets. The microspheres may be coated for controlled release with an enteric coating or may be combined into a fast/slow release combination. [95]

DIFFUCAPS® technology: This technology is nothing but capsule based system containing one or more drug-containing particles (e.g. beads, pellets, granules etc.). Each bead shows pre-programmed rapid or sustained release profile with or without lag time. It has been already discussed in system with erodible, soluble or rupturable membrane section. [96]

CONTIN® technology: Here cellulose polymer and a nonpolar solid aliphatic alcohol constitute molecular coordination complexes between them. At first that polymer is solvated with a polar solvent. Alcohol may be optionally substituted with an aliphatic group. This alcohol is added to the solvated polymer preferably as a melt. After addition it forms the coordination complex having utility as a matrix in controlled release formulations since it has a uniform porosity which may be varied. It is also applicable for designing of controlled release tablets. This technology has sufficient control over drug release to the blood and reduces the chances of unwanted side effects. [97]

CHRONOTOPIC® technology: It is also described in system with erodible, soluble or rupturable membrane system. It is basically drugcontaining core coated with an outer releasecontrolling layer. Both single and multiple-unit dosage forms such as tablets and capsules or minitablets and pellets have been employed as the inner drug formulation. [97]

EGALET® technology: It is a delayed release form consisting of an impermeable shell with two lag plugs, enclosing a plug of active drug in the middle of the unit. After erosion of the inert plugs the drug is released. Time taken to erode the inert plugs determines the lag time. The shells are made of slowly biodegradable polymers (e.g. ethylcellulose) and plasticizers (such as cetostearyl alcohol), while the matrix of the plugs is a mixture of pharmaceutical excipients including polymers like polyethylene oxide (PEO). [98]

CODAS® technology: Chronotherapeutic Oral Drug Absorption System (CODAS) technology is a multiparticular system designed for bedtime dosing. Here nonenteric coating is applied on drug-loaded beads to delay the release of drug up to 5 h. Here release controlling contains mixture of both water-soluble and waterinsoluble polymers. When this dosage form comes in contact with GI fluid water-soluble polymer gets dissolved slowly and pores are formed on the coating layer. Drug diffuses through these resulting pores. Water-insoluble polymer acting as a barrier maintains the controlled release fashion like release of verapamil. [99]

TIMERx® technology: It is hydrogel based controlled release device. This technology can provide from zero order to chronotherapeutic release. It can provide different release kinetic by manipulating molecular interactions. The authors claimed that the "molecular engine" replaces the need for complex processing or novel excipients and allows desired drug release profiles to be "factory set" following a simple formulation development process. Basically, this technology combines primarily xanthan and locust bean gums mixed with dextrose. The physical interaction between these components works to form a strong, binding gel in the presence of water. Drug release is controlled by the rate of water penetration from the gastrointestinal tract into the TIMERx gum matrix, which expands to form a gel and subsequently releases the active drug substance. [99]

PORT® technology: The Programmable Oral Release Technologies (PORT) system is a uniquely coated, encapsulated system that can provide multiple programmed release of drug. It contains a polymeric core coated with a semipermeable, rate-controlling polymer. Poorly soluble drugs can be coated with solubilizing agents to ensure uniform controlled release from the dosage form. In capsule form had gelatin capsule is coated with a semipermeable, rate-controlling polymer. Active medicament mixed with osmotic agent is kept inside capsule shell. A water-insoluble plug is used to seal the capsule shell. Immediate release compartment can be added according to need. [100]

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. [18]

CONCLUSION

The literature review relating to this formulation strongly recommending 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 a drug at right time, right place, and in right amounts, holds good promises of benefit to the patients suffering from chronic problems like asthma, hypertension, arthritis, etc. Immediate release formulation and extended release formulations are not efficient in treating the diseases especially diseases with chronological pathopysiology, for which, pulsatile drug delivery is beneficial. The drug is delivering in this system when its actual concentration is needed as per chronological need, so pulsatile release systems should be promising in the future.

Table-1: Disease Influenced by Chronotherapy [14]

Diseases	Influenced by Chronotherapy
Cardiovascular	Hypertension, angina, myocardial infarction
Neoplastic	Various forms of cancer
Inflammatory	Rheumatoid arthritis, related disorders
Respiratory	Allergic rhinitis, asthma
Gastrointestinal	Peptic ulcer disease

Table-2: Diseases requiring PDDS [33, 34]

Diseases	Chronopharmacological behavior	Drug
Peptic ulcer	Acid secretion is high in afternoon and at midnight.	H2 blocker
Asthma	Precipitation of attack during night or early morning.	B2 agonist, Antihistamine
Hypercholesterolemia	Cholesterol synthesis is higher during night than day	HMG COA enzyme Inhibitor,
Arthritis	Pain in morning(RA) and more pain at Night	NSAIDS and Glucocorticoides
Gout	Increase in uric acid level in morning	Colchicines, Febuxostat, Gold
Cardiovascular diseases	BP is at its lowest during the sleep Cycle and rises steeply during early morning	B2 blocker, ACE inhibitor, calcium Channel blocker
Attention deficiency syndrome	Increase in DOPA level in afternoon	Methylphenidate, Atomoxetin

Table 3: Review of Literature for Pulsatile Drug Delivery System

Drug	Polymer	Remarks	Reference No.
Salbutamol Sulphate	Sodium alginate and ethyl cellulose	The developed system is capable of releasing salbutamol after a 4 h lag period and can be considered as promising delivery system for time-controlled.	84
Tramadol HCl	Eudragit RL 100 and PGE 6000	The lag time of the drug release decreased by increasing the inner swelling layer and increased by increasing the rupturing layer level.	85
Candesartan	Hydroxy propyl methyl cellulose K4M, Eudragit L100-55 and Eudragit S100.	The developed system is capable of releasing salbutamol after a 6 h lag period.	86
Diltiazem	Hydrogel plug and Ethylcellulose	Hydrogel plug showed a lag time of 4-8 hours with release of 83% at the end of 20 hours and followed zero order kinetics.	87
Atorvastatin	Eudragit S100, HPC	The developed system is capable of releasing salbutamol after a 6 h lag period.	88
Atenolol	HPMC K4M and Ethylcellulose	The developed system is capable of releasing salbutamol after a 6 h and 6.5 hr lag period.	89
Lisinopril	HPMC K4M and HPMC K15M	The release mechanism of the tablet followed the Korsmeyer-Peppas equation and a first-order release pattern.	90
Felodipine	HPMC E5, HPMC E15 and HPMC E50	Drug is released as a burst after a lag time (during peak morning hours) giving relief from morning surge hypertension effect.	91
Simvastatin	Eudragit S100	The dissolution of pellets in phosphate buffer 7.4 shows lag time for 4 hrs followed by conventional release of simvastatin.	92
Terbutaline Sulphate	Eudragit S100 and Eudragit S100	The kinetic study data for best formulation followed zero order kinetics.	93

Table-4: Example of FDA approved pulsatile drug delivery systems in market

Technology	Proprietory name, dosage form	API	Diseases	Reference No.
OROS®	CoveraHS: extended release tablets	Verapamil HCl	Hypertension/ increased BP in early morning	94
CEFORM®	Cardizem®LA: extended release tablets	Diltiazem HCl	Hypertension	95
DIFFUCAPS®	Innopran® XL: extended release capsules	Propranolol HCl Verapamil HCl	Hypertension	96
PulsincapTM	PulsincapTM	Dofetilide	Hypertension	94
CONTIN®	Uniphyl®: extended release tablets	Theophyline	Asthma/increased bronchoconstriction in morning	97
CODAS®	Verelan® PM: extended release capsules	Verapamil HCl	Hypertension	99

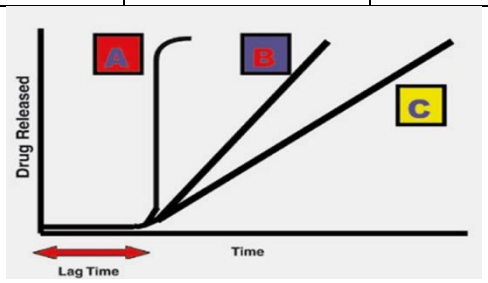

Figure 1: Drug release profile of pulsatile drug delivery system

A-Ideal sigmoidal release and B and C- Delayed release after initial lag time [6, 7]

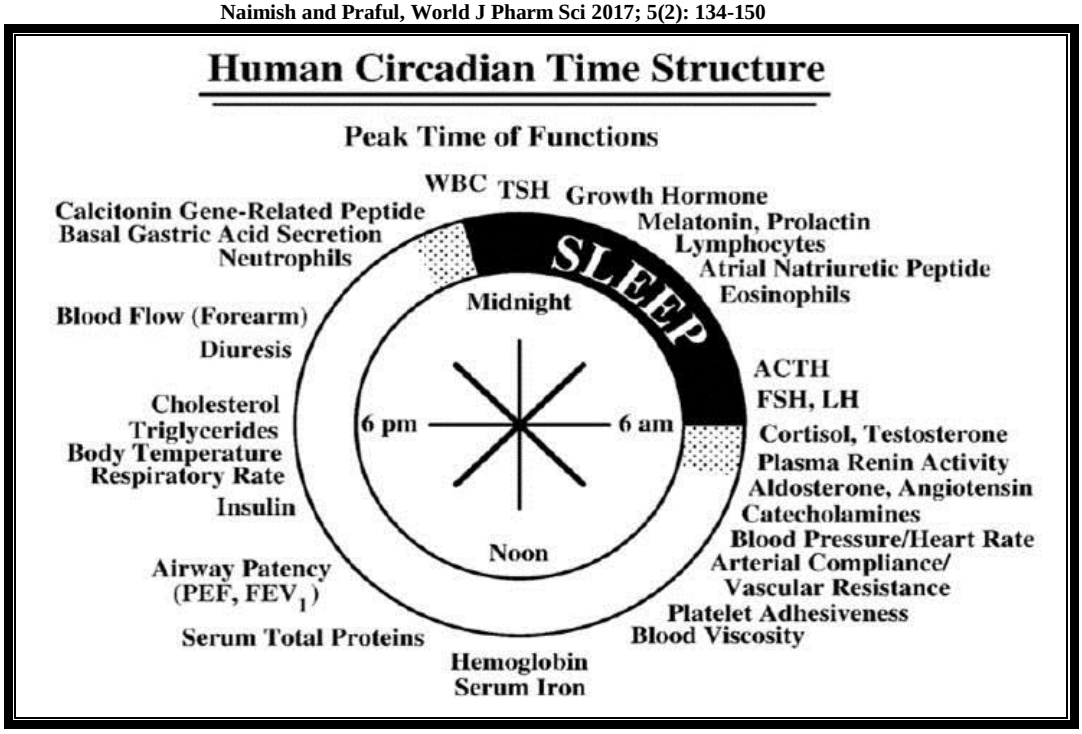

Figure 2: Diseases showing circadian rhythm [16]

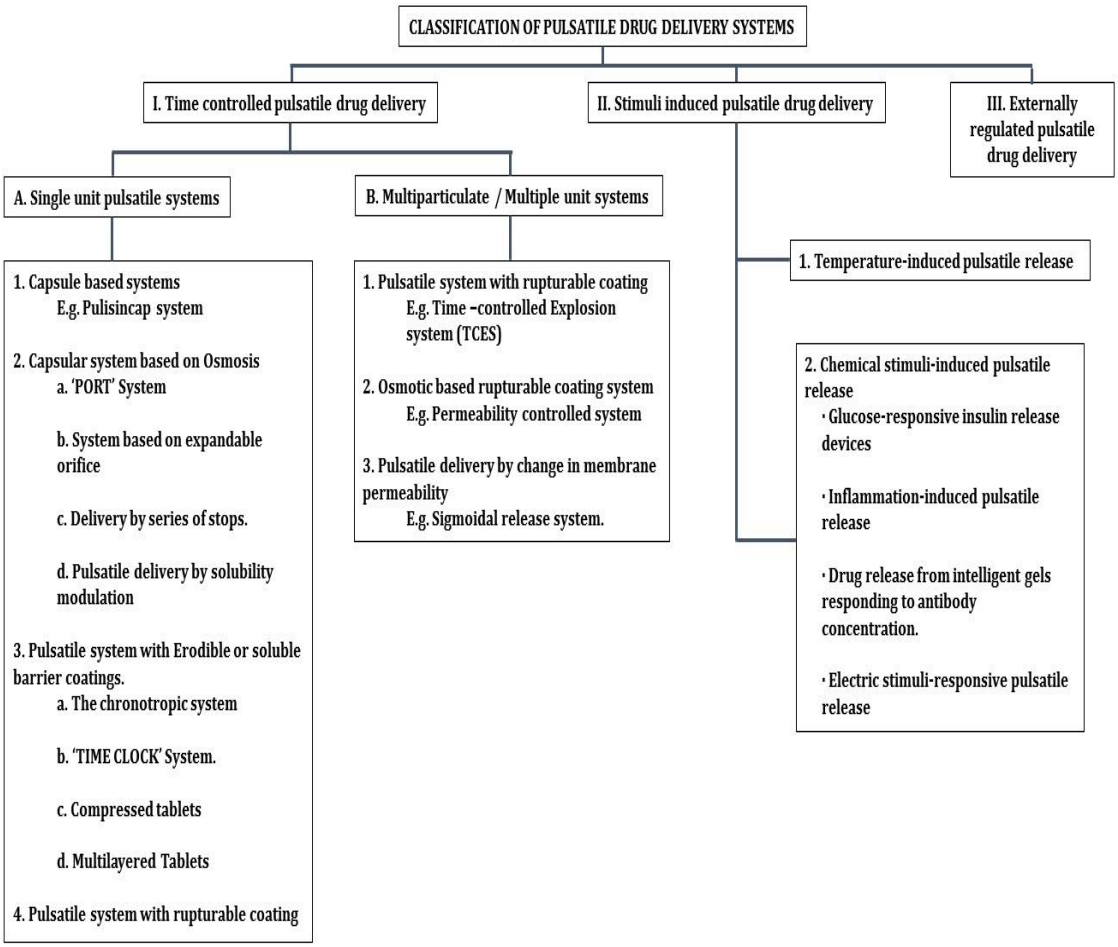

Figure 3: Classification of Pulsatile Drug Delivery System [35]

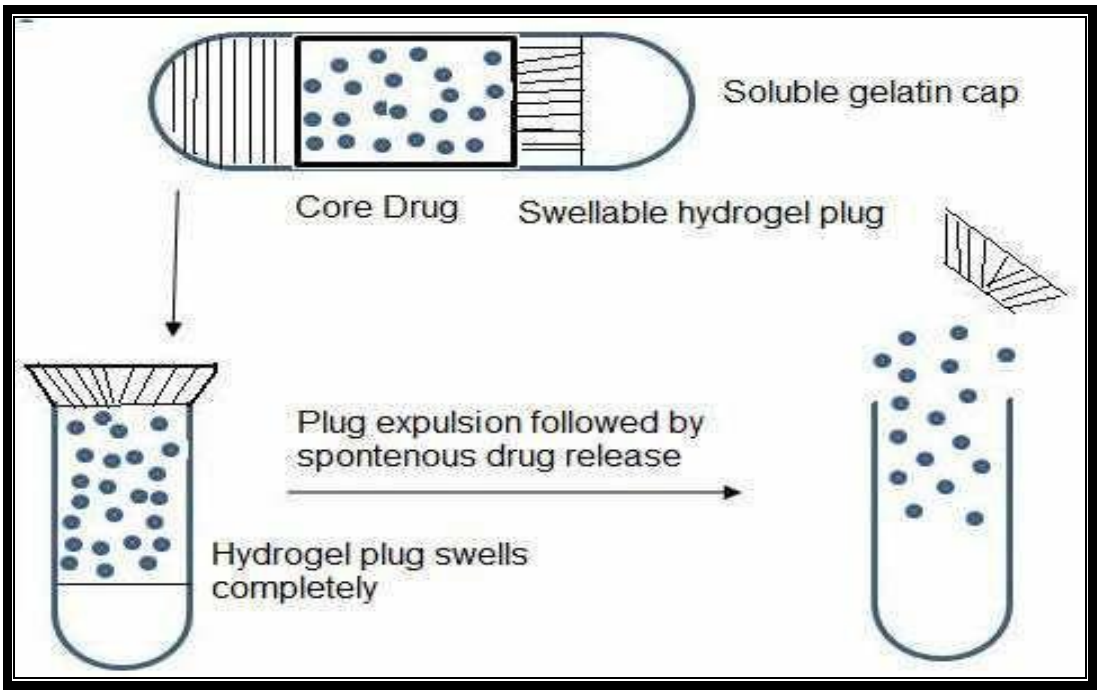

Figure 4: Design of Pulsincap system [36]

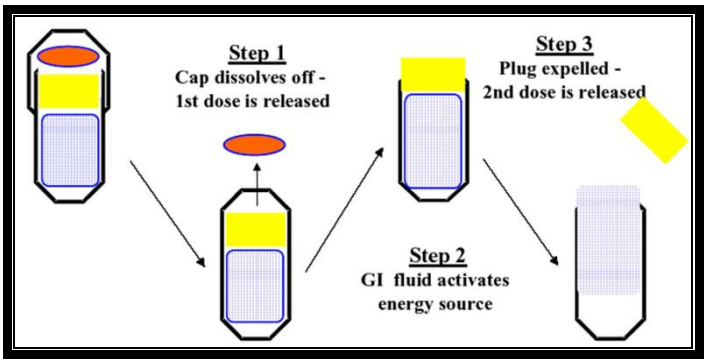

Figure 5: Drug release mechanism from PORT system [42]

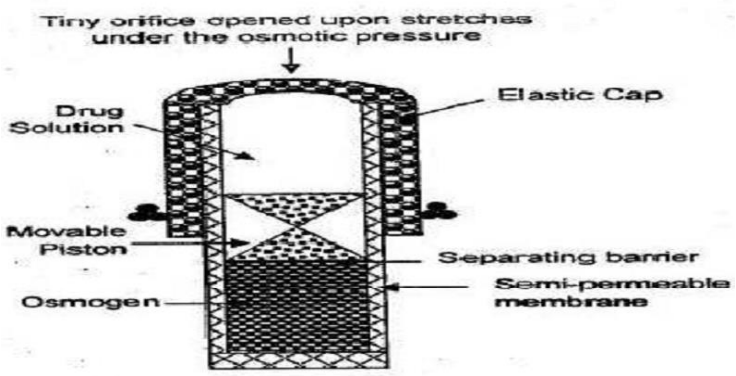

Figure 6: System based on expandable orifice [43]

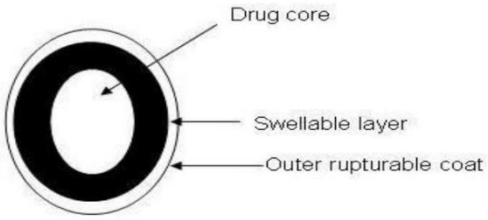

Figure 7: The chronotropic system [52]

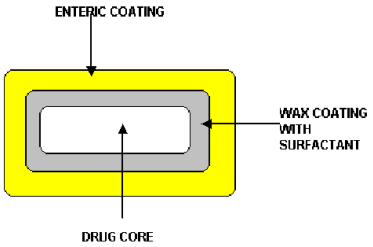

Figure 8: 'TIME CLOCK' System [55]

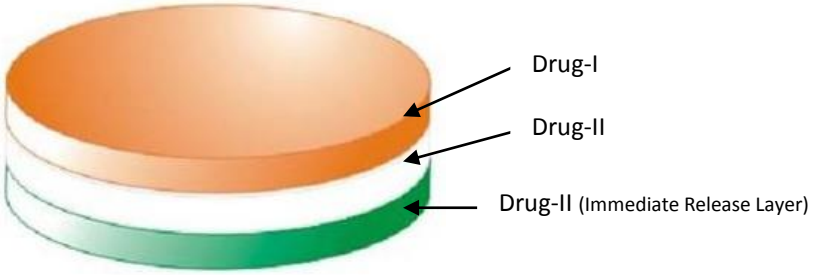

Figure 9: Multilayered Tablet [57]

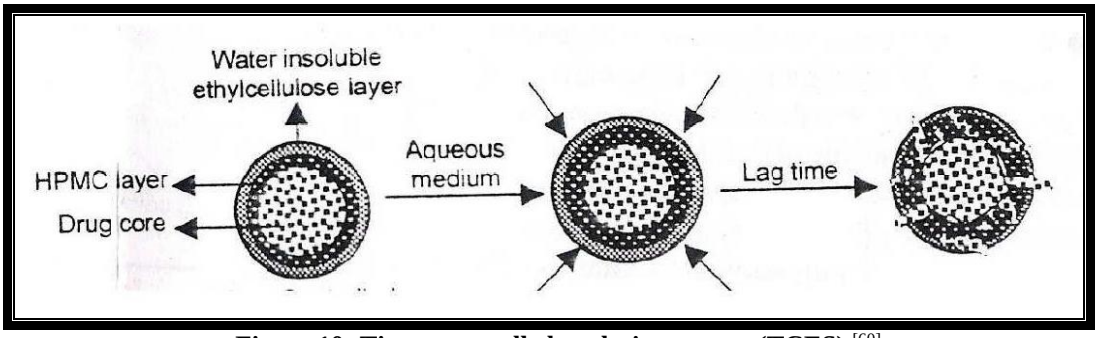

Figure 10: Time –controlled explosion system (TCES) [60]

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