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PULSATILE DRUG DELIVERY SYSTEM: AN OVERVIEW

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ABSTRACT

Current research in the field of drug delivery devices, pulsatile drug delivery system is the most interesting time and site-specific system. This system is designed for chronopharmacotherapy. Thus, to mimic the function of living systems and in view of emerging chronotherapeutic approaches, pulsatile delivery, which is meant to release a drug following programmed lag phase, has increasing interest in the recent years. Diseases wherein pulsatile drug delivery systems are promising include asthma, peptic ulcer, cardiovascular diseases, arthritis, attention deficit syndrome in children, and hypercholesterolemia. In pursuit of pulsatile release, various design strategies have been proposed, mainly including time controlling, stimuli induced, externally regulated and multiparticulate formulations. These systems are beneficial for the drugs having chronopharmacological behavior where night time dosing is required and for the drug having high first pass metabolism effect and having specific site of adsorption in gastrointestinal tract. In the present review article, the novel methods of preparing controlled or extended release formulations which can be successfully used in chronotherapy have been mentioned. These techniques also applied for drugs that require modification of drug release, masking of bitter taste, and protection of volatile substances. These technologies have also been found useful for timed- release dosage forms, as timing release tablets, time clock system and delayed-release tablets.

Keywords: Pulsatile drug delivery systems, circadian rhythms, chronotherapy.

INTRODUCTION

Today, a vast amount of literature reports that biological processes are not constant but vary according to time. Although much of drug delivery research has focused on constant drug release rate due to limitations of delivering drug according to disease rhythmicity, clinical studies show that magnitude of rhythmic differences can be to a great extent and a strong determinant of when during 24 hrs most morbid and mortal event will occur. For many drugs constant release system is not suitable. Drugs not suitable for constant release are used in disease condition that exhibit rhythmic variation within a circadian cycle. For, drugs with decrease bioavailability due to first pass metabolism, gradual release of drug from constant release systems can result in greater degradation. Drugs with more toxic effects, continuous exposure may lead to increased adverse effects. For, drugs which exhibit tolerance, constant exposure decreases drug effect. Modified release dosage forms have acquired a great importance in the current pharmaceutical research and development field. These dosage forms show different release profiles depending on their type. This dosage form is used to describe products that alter the timing and rate of release of drug substance [1].

Various modified release drug products

Extended Release: It leads to two fold reductions in dosing frequency compared to immediate release dosage forms.

(i) Controlled release: This system allows slow drug release over extended period of time but not at predetermined rate.

(ii) Sustained release: This system delivers drug at predetermined rate over a long period.

Delayed Release: This dosage form releases discrete portion of drug at a time other than readily after administration, although one portion may be released promptly after administration.

Targeted Release: These delivery systems deliver drug at or near the intended site of action and may have extended release characteristics.

Repeated Action: This product is designed to release first dose initially, followed by second dose of drug at a later time.

Prolonged Action: This dosage form releases drug slowly and provide continuous supply of drug over an extended period [2].

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Oral delayed DDS, which releases drugs after a programmable period of time, is intended for the therapy of diseases that depend on circadian rhythms. The system consists of a core and a coating. The core is coated with different polymeric barriers by film or compression, and the coating prevents drug release from the core until the polymeric shell is completely swollen or eroded. Better patient compliance and large surface area in the gastrointestinal tract are the two most important advantages of oral drug delivery systems[3]. Assuming that physiological processes and biological functions display constancy over time, much effort had been devoted in the past in developing the drug delivery systems that maintain a flatter plasma level for an extended period of time. However, "chronobiological" studies believe this concept [4].

Chronotherapy

The term "chrono" basically refers to the observation that every metabolic event undergoes rhythmic changes in time. Researchers have concluded that all living organisms are composites of rhythms with varying frequencies that may range from seconds to seasons. Perhaps the best known and studied chronobiologic frequency is the circadian rhythm which approximates the earth's 24-hour rotation around the sun[5]. Researchers have recently concluded that both disease states and drug therapy are affected by a multitude of rhythmic changes that occur within the human body [6].

Chronotherapy coordinates drug delivery with human biological rhythms and holds huge promise in areas of pain management, treatment of asthma, heart disease and cancer. The coordination of medical treatment and drug delivery with such biological clocks and rhythms is termed chronotherapy. The goal of chronotherapeutic is to synchronize the timing of treatment with the intrinsic timing of illness. In contrast, many side effects can be minimized if a drug is not given when it is not needed. A major objective of chronotherapy in the treatment of several diseases is to deliver the drug in higher concentrations during the time of greatest need according to the circadian onset of the disease or syndrome. The chronotherapy of a medication may be accomplished by the judicious timing of conventionally formulated tablets and capsules [7-11].

Circadian rhythms and their implications

Circadian rhythms are self-sustaining, endogenous oscillation, exhibiting periodicities of about one day or 24 hrs. Normally, circadian rhythms are synchronized according to the body's pacemaker clock, located in the suprachiasmic nucleus of the hypothalamus. The physiology and biochemistry of human being is not constant during the 24 hrs, but variable in a predictable manner as defined by the timing of the peak and through of each of the body's circadian processes and functions. The peak in the rhythms of basal gastric and secretion, white blood cells (WBC), lymphocytes, prolactin, melatonin, eosinophil's, adrenal corticotrophic hormone (ACTH), follicle stimulating hormone (FSH), and luteinizinghormone (LH), is manifested at specific times during the nocturnal sleep span. The peak in serum cortisol, aldosterone, testosterone plus platelet adhesiveness and blood viscosity follows later during the initial hours of diurnal activity. Hematocrit is the greatest and airway caliber the best around the middle and afternoon hours, platelet numbers and uric acid peak later during the day and evening. Hence, several physiological processes in humans vary in a rhythmic manner, in synchrony with the internal biological clock (see Fig 1 and 2) [7, 8].

Time controlled drug delivery system based on chronotherapy or chronopharmacology have been investigated together with release rate controlled system for the treatment of diseases such as chemotherapy, neurological disorders, ischemic heart disease, asthma and arthritis. Drug for treatment of such diseases should be administered so as to maintain a therapeutic blood level only at the required time, and hence the drug release behavior should be controlled by rate [10-15]. Diseases where constant drug levels are not preferred, but needs a pulse of therapeutic concentration in a periodic manner acts as a push for the development of "Pulsatile Drug Delivery Systems''[16, 17]. These technologies have the unique characteristic that a drug is released from the formulation after a predetermined lag time [12, 15], Hence, they can be successfully used as a chronotherapeutic drug delivery system.

PULSATILE DRUG DELIVERY SYSTEMS

A Pulsatile drug delivery system delivers drug in rapid and burst manner within a short time period immediately after a programmable lag phase [18]. There are many situations where drug is needed to be released immediately (after bursting the delaying film coat) at specific site. These situations, therefore, compel designing a delayed fast release systems. These systems are mainly appropriate for drugs that are metabolized to pharmacological active compounds, drugs which have long in vivo half lives showing an inherently prolonged duration of action, drugs with very short in vivo half life which require a prohibitively large amount of active ingredients in dosage form, drugs which are required in large doses for therapeutic effect and drugs which are required in very low dose. Additionally a delayed burst release can also be utilized for enhancing absorption, reducing side effects, increasing and decreasing dose [19].

Advantage of pulsatile drug delivery system [19]:

There are many advantages of pulsatile dosage form over conventional dosage form.

- Increases absorption and bioavailability than conventional immediate release or sustained release drug due to its ability to release drug in a burst manner, at target site of absorption.
- Site targeting allows delivery of poorly bioavailable

drugs that would get destroyed in higher GI tract environment e.g. (peptide and protein molecules)

- Reduces dose of drug without decrease in therapeutic effects.
- Decreases side effects.
- Decreases drug interaction due to lower cytochrome P_{450} isoenzymes.
- Decreases food effect (change occurring in bioavailability of drug when given with food).
- Improved compliance.
- Chronotherapy, programmed delayed release provides optimal treatment of diseases.
- Pulse release allows multiple dosing in a single dosage form.
- Allows site specific release for local treatment of diseases. Drug release is not affected by change in pH of the gastrointestinal tract, viscosity of lumen contents, and agitation rate of GI tract.
- The system can be utilized for many solid dosage forms like granules, microspheres, microparticles, tablets, capsules, and pellets.

Disadvantage of pulsatile drug delivery system [20, 21]

- Low drug loading capacity and incomplete release of drug.
- Higher cost of production.
- Large number of process variables.
- Lack of manufacturing reproducibility and efficacy.
- Batch manufacturing process.
- Unpredictable IVIVC.
- Need of advanced technology.

Drug release profiles from pulsatile drug delivery system

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. Such systems are also called time-controlled as the drug released is independent of the environment.

Pulsatile drug delivery systems are gaining a lot of interest and attention these days. These systems have a peculiar mechanism of delivering the drug rapidly and completely after a "lag time," i.e., a period of "no drug release[22].

Modified release dosage forms shows different release profiles depending on their type. The ideal drug release profile of pulsatile drug delivery systems is deplicated in Fig 3.

In this graph, it was aimed to achieve a sigmoid release pattern (a). The characteristic feature of the formulation was a well-defined lag time followed by a drug pulse with the enclosed active quantity being released at once. Thus, the major challenge in the development of pulsatile drug delivery system is to achieve a rapid drug release after the lag time. Often, the drug is released over an extended period of time (patterns b & c in Fig 3)[23].

Methods of Development of Pulsatile Drug Delivery System

Different approaches of pulsatile system are:

I. Time controlled pulsatile drug delivery

- Single unit pulsatile systems
- Multiparticulate / Multiple unit systems

II. Stimuli induced pulsatile drug delivery

III. Externally regulated pulsatile drug delivery

Time controlled pulsatile drug delivery

Single unit pulsatile systems (or) Capsule based systems (or) Pulisincap system

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 [24]. The lag time can be controlled by manipulating the dimension and the position of the plug [25, 26].

Polymers used for designing of the hydrogel plug:

1) Insoluble but 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, glycerol monooleate)

4) Enzymatically controlled erodible polymer (e.g., pectin**)**[27, 28].

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 content of gel-forming polymer (HPMC) and the erodible plug weight[29].

Capsular system based on Osmosis

'PORT' System

The Port system (Fig.5) was developed by Therapeutic system research laboratory Ann Arbor, Michigan, USA, and consists of a capsule coated with a semi permeable 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 [30].

System based on expandable orifice

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 semi permeable capsule supported by an expanding osmotic layer after the barrier layer is dissolved[31].

This system has combined benefit of extended release with high bioavailability. Delivering drug in liquid form is suitable for insoluble drugs, Polypeptides and Polysaccharides[32]. The capsular system delivers drug by the capsule's osmotic infusion of moisture from the body (Fig 6). The capsule wall is made up of an elastic material and possesses an orifice.

As the osmosis proceeds, the pressure within the capsule rises, causing the wall to stretch. 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. For example, elastomers, such as styrene-butadiene copolymer have been suggested. Pulsatile release was achieved after lag times of 1 to 10 hrs. Depending on the thickness of the barrier layer and that of semipermeable membrane [33].

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 [34].

Pulsatile delivery by solubility modulation

These systems contain a solubility modulater 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 (Nacl).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. The modulating agent can be a solid organic acid, inorganic salt or organic salt[35].

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.

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[36-38]. 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 [39].

The lag time is controlled by the thickness and the viscosity grades of HPMC [40]. Both in-vitro and in-vivo lag times correlate well with the appliedamount of the hydrophilic retarding polymer. The system is suitable for both tablets and capsules [41].

'TIME CLOCK' System

The time clock system is a delivery device based on solid dosage form that is coated by an aqueous dispersion. The core is coated at 75°C with aqueous dispersion of a hydrophobic surfactant layer (Beeswax, carnubawax, poly {oxyethylene} - sorbiton monooleate) [42]. A water soluble coat is applied to improve adhesion to the core coat (Fig 8). Once in contact with the dissolution fluid, the dispersion rehydrates and redisperses. The lag time could be controlled by varying the thickness of the film. 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 [43].

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 [44].

Press-coated pulsatile drug delivery systems:

1. Press-coated pulsatile drug delivery systems can be used to protect hygroscopic, light-sensitive, oxygen labile 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.

Multilayered Tablets

Two pulses can be obtained from a three layered tablet containing two drugs containing layers separated by a drug-free gellable polymeric barrier layer (Fig 9). This three-layered tablet is coated on three sides with impermeable ethyl cellulose, and the top portion was left uncoated. Upon contact with dissolution medium, the initial dose incorporated into the top layer was released rapidly from the non-coated surface. The second pulse is obtained from the bottom layer after HPMC layer gets eroded and dissolved[45].

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 [46].

Multiparticulate / Multiple unit systems

Pulsatic system with rupturable coating

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. Upon ingress of water, the swellable layer expands, resulting in rupture of film with subsequent rapid drug release. This release is independent of environmental factors like pH and drug solubility [47].

Osmotic based rupturable coating system:

This system is based on a combination of osmotic and swelling effects. The core contains drug, a low bulk density solid and/or liquid lipid material (eg, mineral oil) and a disintegrant. The core is finally 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 coat [48]. Another system is based on a capsule or tablet composed of a large number of pellets with different release pattern [49]. Each pellet has a core that contains the therapeutic drug and a water-soluble osmotic agent.

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 [50].

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 .These systems are further classified into 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 the polymer undergoes swelling or deswelling phase in response to the temperature which modulate drug release in swollen state [51].

Chemical stimuli induced pulsatile systems

(a) Glucose-responsive insulin release devices: In case of diabetes mellitus there is rhythmic increase in the levels of glucose in the body requiring injection of the insulin at proper time. Several systems have been developed which are able to respond to changes in glucose concentration. One such system includes pH sensitive hydrogel containing glucose oxidase immobilized in the hydrogel. When glucose concentration in the blood increases glucose oxidase converts glucose into gluconic acid which changes the pH of the system. This pH change induces swelling of the polymer which results in insulin release. Insulin by virtue of its action reduces blood glucose level and consequently gluconic acid level also gets decreased and system turns to the deswelling mode thereby decreasing the insulin release. Examples of the pH sensitive polymers include N, Ndimethylaminoethyl methacrylate, chitosan, polyol etc.[52].

(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/reselling characteristics.

Special attention was given to antigen-antibody Complex formation as the cross-linking units in the gel, since such interactions 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 [51,52].

(c) 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. An example of pH dependent polymers includes cellulose acetate phthalate, polyacrylates, and sodium carboxy methyl cellulose. These polymers are used as enteric coating materials so as to provide release of drug in the small intestine [51].

Externally regulated pulsatile drug delivery

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[51, 52].

Examples of some of the diseases are shown in Table

Table 1. Circadian rhythm and manifestation of clinical diseases

S.No	Disease or syndrome	Circadian rhythmicity
1	Allergic Rhinitis	Worse in the morning/upon rising
2	Asthma	Exacerbation more common during the sleep period
3	Rheumatoid Arthritis	Symptoms more common during the sleep period
4	Osteoarthritis	Symptoms worse in the middle/later portion of the day
5	Angina Pectoris	Chest pain and ECG changes more common in early morning
6	Myocardial Infraction	Incidence greatest in early morning
7	Stroke	Incidence higher in the morning
8	Sudden cardiac death	Incidence higher in the morning after awakening
9	Peptic ulcer disease	Worse in late evening and early morning hours

Fig 1. A 24-hrs clock diagram of the peak time of selected human circadian rhythms with reference to the day-night cycle

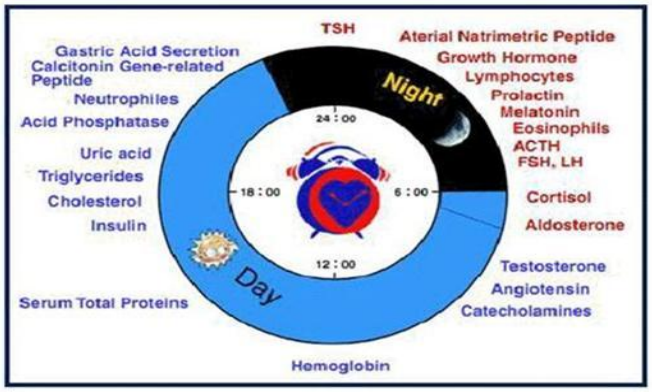


Fig 2. A 24-hrs clock diagram of the peak time selected human circadian rhythms with reference to the day-night cycle

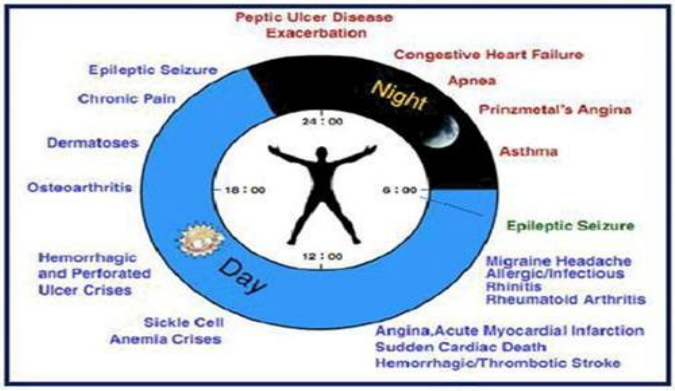


Fig 3. Schematic representation of different drug delivery systems, where (a) sigmoid release after lag time, (b) delayed release after lag time, (c) Sustained release after lag time, (d) extended release without lag time.

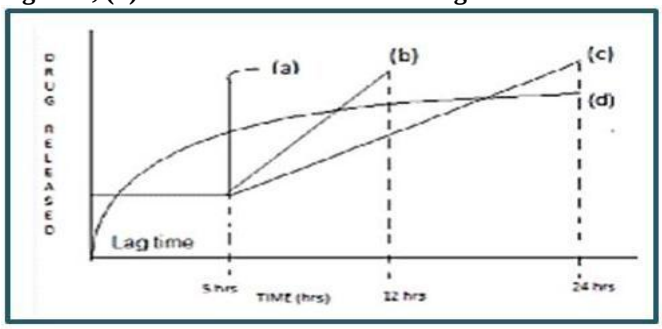


Fig 4. Design of Pulsincap system

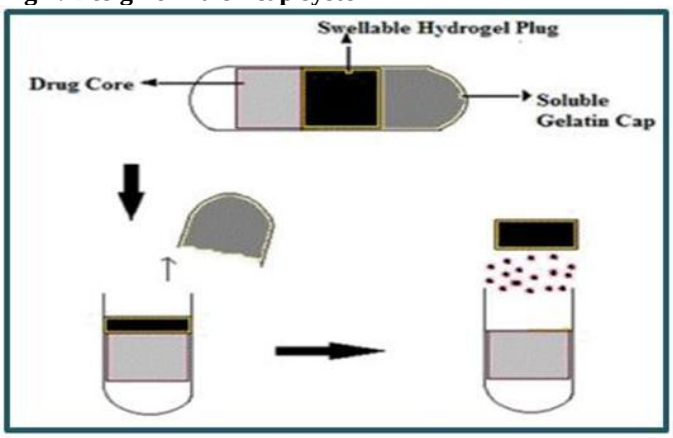


Fig 5. Drug release mechanism from PORT system

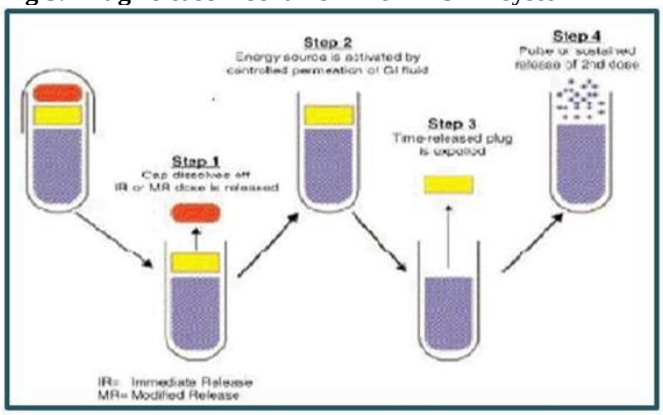


Fig 6. System based on expandable orifice

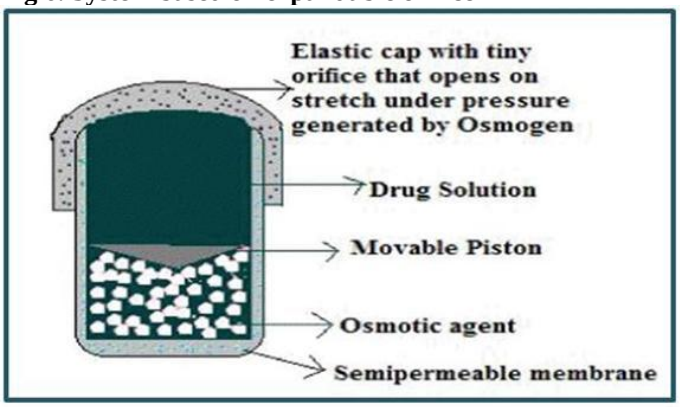


Fig 7. The chronotropic system

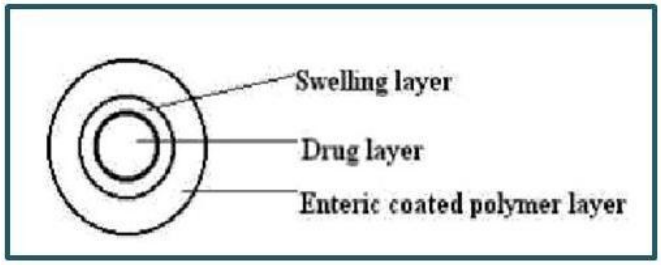


Fig 8. 'TIME CLOCK' System

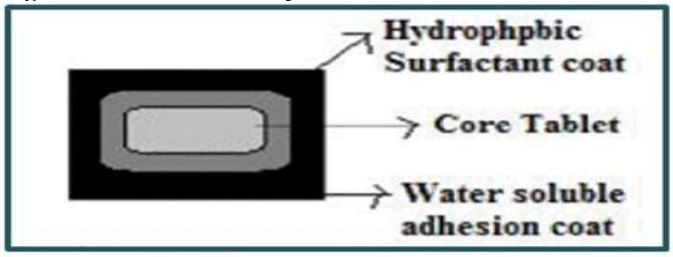


Fig 9. Multilayered Tablets

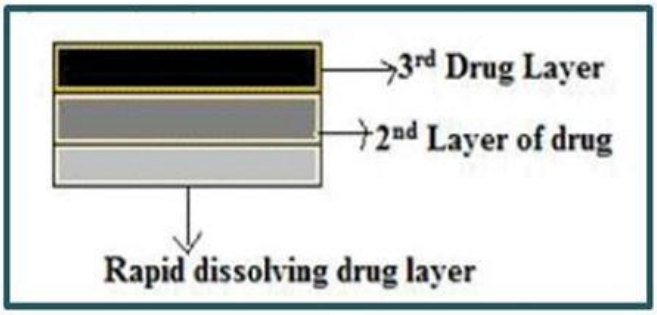
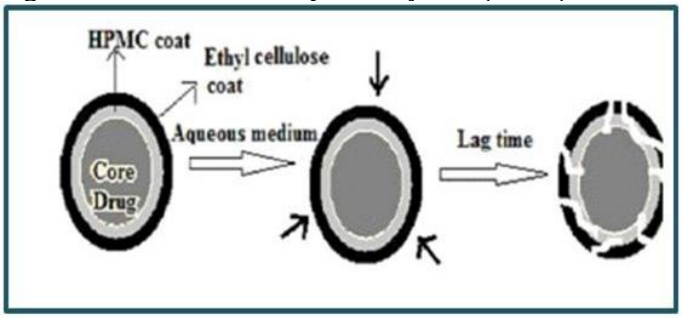


Fig10. Time –controlled Explosion system (TCES)



CONCLUSION

Although sustained and controlled drug delivery systems have gained a lot of success and application in field of medication, these systems fail to deliver drug according to circadian behavior of diseases for which pulsatile systems are beneficial. For successful development of chronotherapeutic dosage form, knowledge of circadian time structure, rhythm in disease pathophysiology or 24 hrs pattern in symptom intensity of chronic medical conditions and chronopharmacology of medication is needed. Significant progress has been made towards achieving pulsatile drug delivery system that can effectively treat diseases with non-constant dosing therapy.

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