Review Article

A Literature Review on Pulsatile Drug Delivery System

Sai Kumar Devireddy*, Leela Prasanna Jonnalagadda
Department of Pharmaceutics, KVSR Siddhartha College of Pharmaceutical Sciences, Vijayawada-52008, Andhra Pradesh state, India.
***Corresponding author's E-mail:** snigdhakumar143@gmail.com

Received: 13-08-2021; **Revised:** 12-01-2022; **Accepted:** 21-01-2022; **Published on:** 15-02-2022.

ABSTRACT

Drugs are very often released in an Immediate or Extend period of time. Pulsatile Drug Delivery Systems, but on the other side, has triggered a lot of attention in recent years because they deliver the drug to the right place at the right time and in the right amount, thus providing spatial, chronological, and smart delivery. which provides greater benefit and patient compliance than conventional dosages. Whenever a constant drug release is not desired, the principle rationale for using pulsatile drug release plays a significant role. After the lag time, a pulse must be designed in such a way that complete and rapid drug release is achieved. Various methods rely on the application of soluble or erodible polymer coatings, such as capsular systems, osmotic systems, single and multiple-unit systems, and use of rupturable membranes have been dealt with in the article. These systems are beneficial for diseases with chrono pharmacological behaviour that necessitate nighttime dosing, drugs with a high first pass effect or GIT site specific absorption, and drugs with a high risk of toxicity or tolerance. Asthma, peptic ulcer, arthritis, cancer, diabetes, epilepsy, hypertension, cardiovascular diseases, attention deficit syndrome in children, and hypercholesterolemia are among the conditions for which PDDS show promising. The classification, advantages, limitations, Recent advances and evaluations and future aspects of the pulsatile drug delivery system were investigated in the current review article.

Keywords: Pulsatile Drug Delivery System, Lag Time, Circadian Cycle, Erodible, Stimuli Induced, Time Controlled, Rupturable coating.

QUICK RESPONSE CODE →

DOI:
10.47583/ijpsrr.2022.v72i02.002

DOI link: http://dx.doi.org/10.47583/ijpsrr.2022.v72i02.002

INTRODUCTION

A number of studies clearly demonstrates that biological processes are not constant but change with time. Spite of the fact that much drug delivery research has concentrated on maintaining a constant medication release rate because to the difficulties of delivering drugs according to diseases rhythmicity, Clinical investigations reveal that the magnitude of rhythmic differences can be a strong determinant of when the most morbid and mortal events will occur throughout a period of 24 hours. The steady release system is ineffective for many drugs. In disease conditions that exhibit rhythmic variation within a circadian cycle, drugs that are not suitable for steady release are used. For drugs with a decrease bioavailability due to first-pass metabolism, delayed drug release from constant-release systems can lead to even further degradation. Continuous exposure to drugs with more harmful effects may lead to an increase in adverse effects. Constant exposure to drugs that exhibit tolerance decreases the drug's effect.

Modified release dosage forms had a significant impact on current pharmaceutical research and development field. These dose forms have different release profiles depending on their type. This dose form refers to the product that modify the timing and rate at which a drug substance is released[1]. The rapid and transient release of a specific amount of drug molecules in a short period of time preceding a predetermined off-release phase, i.e., lag time, is referred to as a pulsatile drug delivery system (PDDS)[2]. Depending on the formulation parameters illustrated in Figure 1[3], pulsatile delivery systems may provide a prompt and quantitative, repetitive or prolonged release pattern after the lag phase.

There are numerous circumstances in which a drug must be released immediately (after the bursting of the delayed film coat) at a specific site. As a result, these situations require the development of delayed quick release systems. These systems are appropriate for drugs that are metabolized to pharmacological active compounds, drugs with long in vivo half-lives which have an inherently prolonged duration of action, drugs with very short in vivo half-lives that require a prohibitively large amount of active ingredients in dosage form, drugs that can be administered in large dosages for therapeutic efficacy and drugs that will be administered in very small doses. A delayed burst release can also be used to enhance absorption, reduce the side effects, and increase and decrease dosing[4].

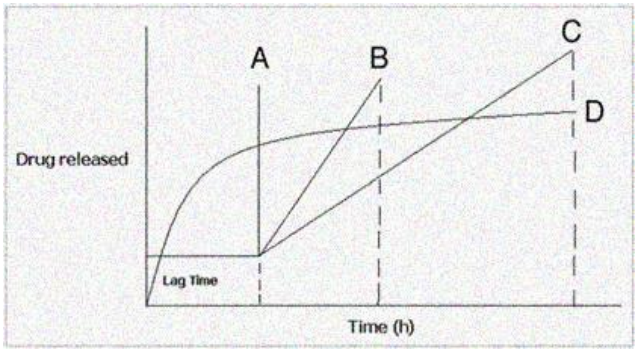

Figure 1: Drug release profiles: (a) Sigmoidal release after lag time, (b) delayed-release after lag time, (c) sustained release after lag time, and (d) extended-release without lag time.

ADVANTAGE OF PULSATILE DRUG DELIVERY SYSTEM

Pulsatile dosage forms have a number of advantages over traditional dosage forms.

1. Increases absorption and bioavailability than conventional immediate or sustained release drugs by permitting the drug to be released in a burst at the absorption site[5].
2. Site targeting enables for the delivery of drugs that are poorly bioavailable and would be degraded in a higher GI tract environment, such as antibiotics (peptide and protein molecules).
3. Reduces drug dosage without reducing therapeutic effects[6].
4. Improved compliance
5. Reduced side effects.
6. Due to lower cytochrome P450 isoenzymes, drug interactions are reduced.
7. Chronotherapy, or programmed delayed release, is a helpful technique for diagnosing diseases[6].
8. Multiple dosing in a single dosage form is possible with pulse release.
9. Allows for disease treatment at a specified location.
10. Drug release is unaffected by changes in GI tract pH, lumen viscosity, and agitation rate of GI tract[7].
11. The system can be used to make granules, microspheres, microparticles, tablets, capsules, and pellets, on several solid dosage forms.

LIMITATIONS OF PULSATILE DRUG DELIVERY SYSTEM

Pulsatile drug delivery systems have certain limitation,

1. In the case of a multiparticulate pulsatile drug delivery system, there seem to be multiple manufacturing steps[8].
2. Drug load is low.
3. A release which is incomplete.
4. In-vivo variability in a pulsatile drug delivery system with a single unit[8].

CLASSIFICATION OF PULSATILE DRUG DELIVERY SYSTEMS

Pulsatile drug delivery system can be broadly categorized into three classes[9];

I. Time controlled pulsatile drug delivery.

II. Stimuli induced pulsatile drug delivery.

III. Externally regulated pulsatile drug delivery

I. TIME CONTROLLED PULSATILE DRUG DELIVERY

A. Single Unit Pulsatile Systems

1. Capsule Based Systems: The majority of single-unit systems are developed as capsules form. The drug is released after the lag time is controlled by a plug that is pushed away by swelling or erosion[10]. Pulsincap (Figure. 2) is one such method that consists of a water insoluble capsule enclosing the drug reservoir and was developed by R. P. Scherer International Corporation in Michigan, United States. When this capsule comes into contact with the dissolution fluid, it expands, and the plug pushes itself outside the capsule after a lag time, and releasing the drug rapidly. The lag time can be controlled by adjusting the plug's dimensions and position. The following polymers were utilized to develop the hydrogel plug[11-12].

1. Polymers that are soluble but permeable and swellable[13] (e.g., polymethacrylates)
2. Compressed erodible polymers (e.g., hydroxypropyl methyl cellulose, polyvinyl alcohol, Polyethylene oxide)
3. Melted polymers that have congealed (e.g., saturated polyglycolated glycerides, glyceryl monooleate)
4. Erodible polymer with enzymatic control[13] (e.g., pectin).
5. The Pulsincap device is made up of an impermeable capsule body that contains the drug and is sealed with a hydrogel plug. This plug swells in GI fluid and then exits away, delivering drug after a predetermined lag time, which is controlled by the thickness of the hydrogel plug[14].
6. An erodible alternative to the Pulsincap plug is available[14].

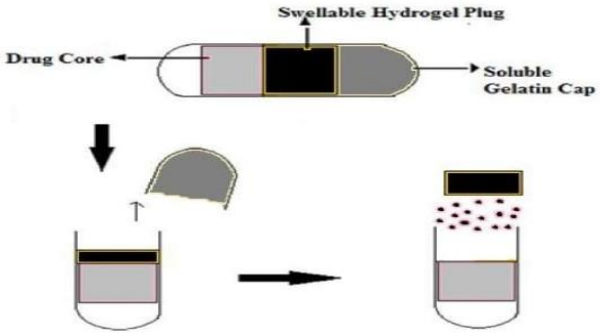

Figure 2: Schematic of Pulsincap dosage form

2. Capsular System Based on Osmosis:

a. 'PORT' System: Therapeutic system research laboratory in Ann Arbor, Michigan, USA, developed the Port system Figure 3, which consists of a capsule coated with a semipermeable membrane. An insoluble plug containing an osmotically active ingredient and the drug formulation was found inside the capsule[15]. When this capsule came into contact with the dissolution fluid, the semipermeable membrane permitted water to pass through, causing pressure to build up and the insoluble plug to expel after a lag time. The pulsatile port system was used to deliver methylphenidate, which is used to treat attention deficit hyperactivity disorder. This technique avoided dosing a second time, which was advantageous for schoolchildren during the day.

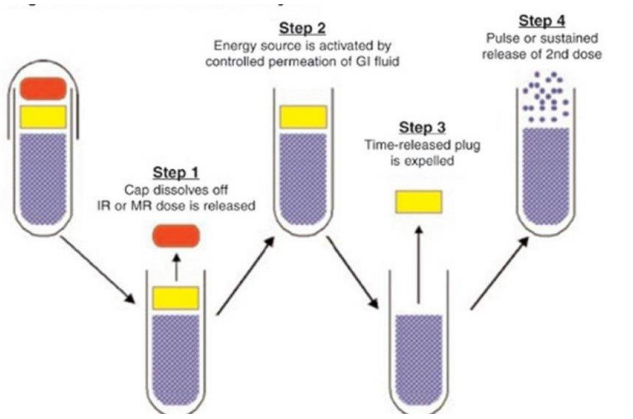

Figure 3: Drug release mechanism from PORT system

b. System Based on Expandable Orifice: An osmotically driven capsular system was developed to deliver the drug in liquid form. Once the barrier layer is dissolved, the liquid drug is absorbed by highly porous particles, which then release the drug through an orifice in a semipermeable capsule supported by an expanding osmotic layer[16]. When the elastic wall relaxes, the drug flow through the orifice essentially stops, but when the elastic wall distends beyond a threshold value, the orifice expands sufficiently to allow drug release at the required rate (Figure 4). Elastomers like styrene-butadiene copolymer are good instance[17-18].

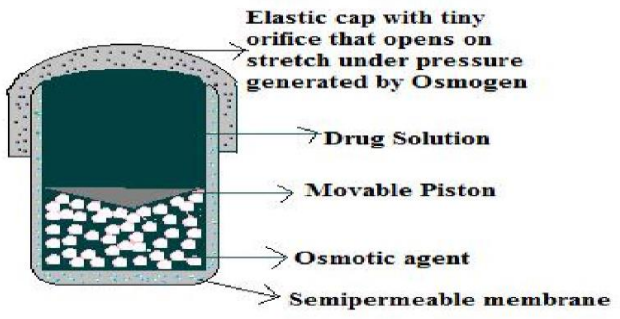

Figure 4: System based on expandable orifice

c. Delivery by Series of Stops: This system is intended for capsules that can be implanted. A drug and a water absorptive osmotic engine are arranged in compartments separated by a moveable partition in the capsule. The pulsatile delivery is accomplished through a series of stops along the capsule's inner wall. These stops block the movement of the partition, but as the osmotic pressure builds above a threshold level, they are overcome one by one[19].

d. Pulsatile delivery by solubility modulation: A solubility modulator is included in these systems, which facilitates for pulsed drug delivery. The system was developed specifically for the administration of salbutamol sulphate[20]. The drug (salbutamol sulphate) and a modulating agent are both present in the compositions (sodium chloride). The concentration of NaCl was less than that required to maintain saturation in a fluid entering the osmotic device. The drug solubility determines the pulsed delivery system. Salbutamol is soluble in water at 275 mg/ml and 16 mg/ml in a saturated NaCl solution, whereas NaCl is soluble in water at 321 mg/ml and has a saturation solubility of 320 mg/ml[21-22].

3. Pulsatile System with Erodible or Soluble Barrier Coatings: The majority of pulsatile drug delivery systems are barrier-coated reservoir devices. The barrier erodes or dissolves when a certain period of time has passed, and the drug is released rapidly from the reservoir core. The lag time is determined by the coating layer thickness[23].

a. The Chronotropic System: The Chronotropic system consists a drug-containing core is coated with hydrophilic swellable hydroxypropyl methyl cellulose (HPMC), which causes a lag in the onset of release. Furthermore, the variability in stomach emptying time can be avoided by using an outer gastric-resistant enteric film, and a colon-specific release can be obtained by relying on the relative reproducibility of small intestinal transit time[24]. The thickness and viscosity grades of HPMC determine the lag time[25]. The applied amount of the hydrophilic retardant polymer correlates well with both in-vitro and in-vivo lag times. Both tablets and capsules can be used in this system[26].

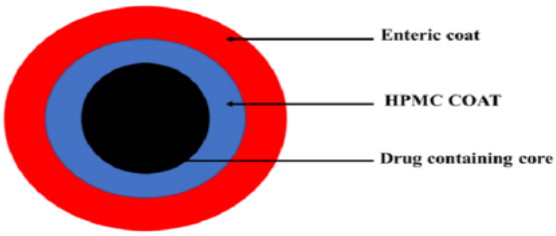

Figure 5: The chronotropic system

b. 'TIME CLOCK' System: The thickness of the film could be modified to alter the lag time. The core immediately releases the drug after the lag time, which is the time required for rehydration. This system has generated consistent results in vitro and in vivo. Gamma scintigraphy was used to investigate the influence of a low-calorie and a high-calorie meal on the lag time. The mean drug release lag time was 345 and 333 minutes respectively[27-28].

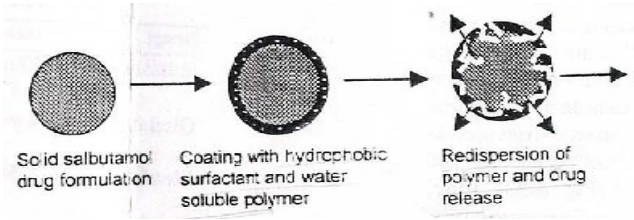

Figure 6: TIME CLOCK' System

c. Compressed tablets: Compression coating eliminates the requirement for coating solutions by compressing both the core and the coat directly. The initial dose is provided by the outer tablet of the compression-coated tablet, which disintegrate rapidly in the stomach, while the inner layer is formulated with components that are insoluble in gastric media but released in the intestinal environment. This could be done with a cellulose derivative. On a laboratory scale, compression is simple. The main drawbacks of this technique are the vast amounts of coating materials required and the difficulty in accurately positioning the cores. Advantages of Press-coated pulsatile drug delivery devices include the ability to protect hygroscopic, light-sensitive, acid-labile drugs, as well as the fact that they are simple and inexpensive to manufacture[29].

d. Multilayered Tablets: A three-layered tablet with two drug-containing layers separated by a drug-free gellable polymeric barrier layer can produce two pulses (Figure 7). The top portion of this three-layered tablet was left uncoated while the other three sides were coated with impermeable ethyl cellulose. When the non-coated surface came into contact with the dissolution media, the initial dose incorporated into the top layer was rapidly released. After the HPMC layer has been eroded and dissolved, the second pulse is retrieved from the bottom layer. The appearance of the second pulse is determined by the rate at which the barrier layer gels or dissolves. Ethyl cellulose, cellulose-acetate propionate, methacrylic polymers, acrylic and methacrylic co-polymers, and polyalcohol's are examples of coating materials. cellulose derivatives such as HPMC, methyl cellulose, and polyvinyl alcohols of various molecular weights are examples of gelling polymers[30-31].

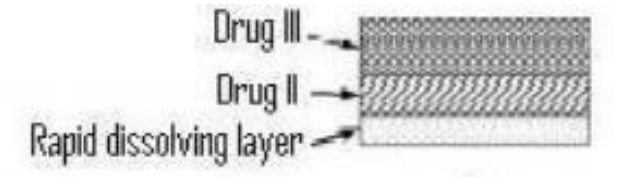

Figure 7: Multilayered Tablet

4. Pulsatile System with Rupturable Coating: The disintegration of the coating is vital for drug release in these systems. To produce the pressure required for the coating to rupture, effervescent excipients, swelling agents, or osmotic pressure can be employed. In a tablet core coated with ethyl cellulose, an effervescent mixture of citric acid and sodium bicarbonate was combined. The coating ruptured as a result of the carbon dioxide generated in the process of the water penetration into the core, leading to pulsatile drug release. The release may be governed by the coating layer's mechanical properties[32].

a. Pulsatile System Based on Rupturable Coating: In this multiarticulate system, the drug is coated on non-pareil sugar seeds, followed by a swellable layer and an insoluble top layer[33-35]. Super disintegrants such sodium carboxymethyl cellulose, sodium starch glycollate, and L hydroxypropyl cellulose are among the swelling agents employed. polyvinyl acetate, polyacrylic acid, and polyethylene glycol are example of polymers., etc.

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

b. Osmotic Based Rupturable Coating System: The osmotic and swelling effects are combined in this system. The core was composed of the drug, a low bulk density solid and/or liquid lipid material such as mineral oil, and a disintegrant. The cellulose acetate was then coated to the core. Water penetrates the core when immersed in an aqueous media, displacing lipid material. Internal pressure rises once lipid material is depleted until a critical tension is achieved, leading the coating to burst[36].

c. Pulsatile Delivery by Change in Membrane Permeability: The presence of different counter-ions in the medium can influence the permeability and water uptake of acrylic polymers containing quaternary ammonium groups[37]. On the basis of this ion exchange, several delivery systems have been developed. Eudragit RS 30D is reported to be the preferred polymer for this application. The polymer side chain usually contains a positively polarized quaternary ammonium group, which is always accompanied by negative Hydrochloride counter-ions. Since the ammonium group is hydrophilic, it facilitates the interaction of the polymer with water, modifying its permeability and permitting controlled water permeation of the active core. This characteristic is essential for achieving an accurate lag time[38].

II. STIMULI INDUCED PULSATILE DRUG DELIVERY

After stimulation by any biological factor, such as temperature, or any other chemical stimuli, the drug is released in these systems. On the basis of stimulation, these systems are further classified into temperature induced systems and chemical stimuli induced systems.

1. Temperature-Induced Pulsatile Release: Thermoresponsive hydrogels have been investigated as potential drug carriers for stimuli-responsive drug delivery systems[39-41]. Thermoresponsive, discontinuous swelling / deswelling phases: swelling at temperatures below 328 C, while shrinking above this temperature have been seen in poly (N-isopropylacrylamide) (PIPAAm) cross-linked gels. The characteristics and biological interests of thermoresponsive polymeric micelle systems, as reviewed by Kataoka et al.[42], make polymeric micelles a noteworthy choice as drug carrier for the treatment of cancer. The amphiphilic block copolymers in the polymeric micelle have a hydrophobic core and a hydrophilic corona.

Between 4 and 378 degrees Celsius, a temperature gradient triggered an on–off drug release regulation from PIPAAm PBMA micelles.

2. Chemical Stimuli-Induced Pulsatile Release

a. Glucose-Responsive Insulin Release Devices: Diabetes mellitus is caused by a reduction in or absence of insulin production from pancreatic islets. Patients with diabetes mellitus suffer a long-term decline in the efficiency of several organs, including occasional loss of vision. Several systems that can respond to variations in glucose concentration have previously been developed. One such system is a pH-sensitive hydrogel containing glucose oxidase immobilized in the hydrogel. Glucose oxidase converts glucose to gluconic acid when blood glucose concentrations rise, then changing the pH of the system. The polymer swells as a result of the pH change, resulted in insulin release. Insulin reduces blood glucose levels and, as a result, gluconic acid levels, and the system switches to a deswelling mode, decreasing insulin secretion. Glucose oxidase (GOD) is a catalytic enzyme that catalyzes the oxidation of glucose. Ishihara et al. used this reaction to create two types of gel membrane systems to control insulin permeability. Separately, they prepared and nicotinamide immobilized gel membranes. pH sensitive polymers include N, N-dimethyl aminoethyl methacrylate, chitosan, polyol etc. are good Instances[43-44].

b. Inflammation Induced Pulsatile Release Device: When injured sites are subjected to physical or chemical stress, inflammation occurs. These inflammation-responsive cells produce hydroxyl radicals during inflammation. Yui and colleagues worked on inflammatory-induced hydroxyl radicals and developed drug delivery systems that responded to the radicals and degraded in a controlled manner. They used hyaluronic acid (HA), which is degraded by hyaluronidase or free radicals. In a healthy person, the amount of HA degraded by hyaluronidase is very low. When HA is injected in inflammatory areas, however, hydroxyl radical degradation is usually dominant and rapid. Thus, anti-inflammatory drug-incorporated HA gels as innovative implanted drug delivery devices can be used to treat patients with inflammatory diseases like rheumatoid arthritis[45].

c. Drug Release from Intelligent Gels Responding to Antibody Concentration. In the body, there are many wide varieties of bioactive compounds. Novel gels have recently been produced that respond to changes in bioactive compound concentrations by changing their swelling/deswelling characteristics. The introduction of stimuli responsive cross-linking structures into hydrogels was the focus of Miyata and colleagues. Because specific antigen recognition of an antibody can provide the basis for the manufacture of a new device, special attention was paid to antigen antibody complex formation as the cross-linking units in the gel[46].

d. pH Sensitive Drug Delivery System: Two components are included in this type of pulsatile medication delivery system, one component of this sort of pulsatile drug delivery system is immediate release, while the other is pulsed release, which releases the medication in reaction to a change in pH. In the case of a pH-dependent system, the fact that different pH environments exist at different parts of the gastrointestinal tract has been exploited. The drug release at a specific place can be accomplished by selecting pH dependent polymers. Polyacrylates, cellulose acetate phthalate, and sodium carboxy methyl cellulose are some examples of pH-dependent polymers. These polymers are employed as enteric coating materials in the small intestine to facilitate drug release.

d. Electric Stimuli-Responsive Pulsatile Release: The development of electronically assisted drug delivery technologies has been helped by advances in several technologies, such as microelectronics and micromachining, as well as the potential need for chronotherapy. Iontophoresis, infusion pumps, and sonophoresis are examples of these technologies. Several techniques for preparing electric stimuli-responsive drug delivery systems using hydrogels have also been described in the literature. Kishi et al[47]. used the electrically stimulated swelling/deswelling characteristics of polyelectrolyte hydrogels to develop an electric stimulation triggered drug release system. They used a chemo mechanical system with a drug model embedded in a polyelectrolyte gel structure. When an electric stimulation was turned on and off, these gels swelled and shrank in a reversible manner. As a result of the electric stimuli-induced gel contraction and solvent flow, drug molecules in polyelectrolyte gels may be squeezed out. Poly (sodium acrylate) microparticulate gels containing pilocarpine as a model drug were prepared to elucidate this mechanism[48].

III. EXTERNALLY REGULATED PULSATILE DRUG DELIVERY

Another technique for releasing drugs in a pulsatile manner is to use externally regulated systems, in which drug release is programmed by external stimuli such as magnetic, ultrasound, electrical effect, and irradiation. Magnetic beads are used in the implant of a magnetically regulated system. Drug release occurs due to magnetic beads when a magnetic field is applied.

Recent Advances in the Pulsatile Drug Delivery

The Pulsatile drug delivery system's primary objective is to deliver the drug in larger concentrations when it's most needed and lower concentrations when it's least needed, hence minimizing unwanted side effects. The following sections discuss the various technologies were used in the development of a Pulsatile drug delivery system[49].

1. CONTIN® Technology: A molecular coordination complex is formed between cellulose polymer and a nonpolar solid aliphatic alcohol. Initially, a polar solvent is employed to dissolve the polymer. An aliphatic group may be substituted with alcohol if needed. This alcohol is preferably added as a melt to the solvated polymer. It forms the coordination complex after being added, and

because it has a uniform porosity which can be modified, it can be used as a matrix in controlled release formulations. It's also useful for manufacturing controlled-release tablets. This technology allows for accurate control the drug release into the bloodstream, reducing the risk of adverse effects[50].

2. OROS® Technology: Osmotic agents are used in this technology to deliver predetermined, controlled drug delivery to the gastrointestinal tract. Covera- HS®, a novel antihypertensive drug, was developed using this technology, particularly the OROS® delayed push pull™ mechanism, commonly known as controlled onset extended release (COER). This allows for the release of verapamil to be delayed overnight, preventing an increase in blood pressure in the morning[51].

3. CODAS® Technology: CODAS® (chronotherapeutic oral drug absorption system) is a multi-particular system that is dosed at bedtime and delays drug release for 4-5 hours. The non-enteric coating of the drug-loaded beads provides the delay. Verapamil extended-release capsules Verelan® PM were developed using this technology[52].

4. CEFORM® Technology: This approach assists in the development of microspheres of uniform size and shape. It is based on a process known as melt spinning, in which a combination of biodegradable polymers or bioactive agents is processed with a combination of temperature, thermal gradients, mechanical forces, flow, and flow rates. Tablet capsules, suspensions, and sachets are all possible forms of microspheres. It's also possible to coat it for controlled release. Cardizem® LA, a 1-day diltiazem chronotherapeutic drug delivery system, was developed using this technology[53].

5. DIFFUCAPS® Technology: This is a capsule-based system that contains one or more drug-containing particles (e.g., beads, pellets, granules etc.). Each bead has a pre-programmed rapid or sustained release profile, with or without lag time. It has been discussed that the system having an erodible, soluble, or rupturable membrane. This method was employed to manufacture Innopran® XL, a hypertension drug that contains Propranolol[53].

6. Chrono modulated infusion pumps: Melodie®, Panomat®, Programmable synchromed®, V5 infusion and Rhythmic® pumps are some of the Pulsatile drug delivery infusion pumps on the market. Portable pumps are typically light in weight (300-500 g) to allow easy portability and accurate drug delivery. In the case of insulin therapy, an implantable infusion pump with an insulin reservoir is surgically inserted in the left upper or lower quadrant of the abdomen's subcutaneous tissue. Insulin is delivered intraperitoneally via a catheter that passes from the pump through the muscle layers and into the peritoneal cavity, where it floats freely. By introducing a needle through the skin into the pump, this insulin-containing reservoir is refilled once a month or every three months at the physician's office. The patient adjusts the dose within the range set by the physician using radiotelemetry and an electronic device held over the pump[54]. Because of the vast surface area and well-vascularized nature of the peritoneum route, absorption is faster than subcutaneous injection. The regulation of blood sugar is improved. The disadvantage is that it can cause insulin delivery to be reduced due to catheter blockage. Pumps are used in the treatment of diseases such as cancer and diabetes[54].

7. TIMERx® Technology: It is a controlled release device based on hydrogel. This technique is capable of delivering anything from zero order to chronotherapeutic release. By modifying molecular interactions, it can provide different release kinetics. According to the authors, the "molecular engine" eliminates the need for complex processing or novel excipients, allowing desired drug release profiles to be "factory set" following a simple formulation development process. Basically, xanthan and locust bean gums are combined with dextrose in this technology. In the presence of water, the physical interaction between these components creates a strong, binding gel. Drug release is regulated by the rate of water penetration from the gastrointestinal tract into the TIMER® gum matrix, which swells to create a gel and then releases the active therapeutic component[55].

9. Other CR erodible polymers: In chon modulated drug delivery systems, erodible polymers are commonly employed. An erodible tablet made of insoluble dibasic calcium phosphate and gel-forming HPMC excipient was used to seal the drug inside the insoluble capsule body. In summary, drug release can be controlled according to the requirements of biological rhythm in a given disease state by carefully selecting and combining polymeric drug carriers with different erosion/degradation kinetics, or by modifying the interaction energy between the drug and the polymer[56].

10. Controlled-release microchip: This microfabrication technology could be employed in the development of a Pulsatile drug delivery system. With enhanced drug release kinetic control to match biological parameters[55].

11. PULSYS™: This technology was used to develop an amoxicillin chronotherapeutic system. Antibiotics are more efficient against fast-growing bacteria; therefore, this technique was developed. When bacteria are exposed to an immediate release system, they go into dormancy, whereas a pulsatile system is more efficient since the drug is released in pulses at regular intervals, which prevents bacteria from going into dormancy. Pulsatile systems have been shown to be more effective in preclinical investigations[56].

12. Spheroidal Oral Drug Absorption System (SODAS): The production of controlled release beads is the basis of this technique and is characterized by its inherent flexibility, which promote the formation of customized dosage forms that immediately respond to the needs of individual drug candidates. SODAS can provide a variety of customized drug release profiles, such as immediate drug release

followed by sustained release for a fast onset of action that lasts for 24 hours. However, if drug release is delayed for a few hours, the opposite scenario can be achieved. Pulsatile release is another possibility, in which a once-day dosage form can resemble many daily doses by releasing the drug in discrete bursts throughout the day[56].

13. The Intestinal Protective Drug Absorption System (IPDAS): This technology is a multi-particulate tablet with a high density that has been intended to treat gastrointestinal irritants. The IPDAS® technology consists of a tablet that is compressed from a large number of high density-controlled release beads. An IPDAS® tablet rapidly disintegrates and disperses drug-containing beads in the stomach, which then pass into the duodenum and through the gastrointestinal tract in a controlled and gradual manner, regardless of feeding condition. The active ingredient is released from the multi particulates by diffusion, which occurs either through the polymeric membrane or the micro matrix of polymer/active ingredient formed in extruded or Spheronized multi particulates.

IPDAS® technology provides intestinal protection due to the multi-particulate nature of the formulation, which ensures that the irritating drug is dispersed widely throughout the gastrointestinal tract. The IPDAS® technology is used in Naprelan®, a drug marketed in the United States and Canada. This innovative controlled-release formulation of naproxen sodium is intended for the treatment of both acute and chronic pain[57].

14. GEOCLOCK® Technology: In order to provide a pH-independent lag time prior to core drug delivery at a predetermined release rate, Geoclock® tablets contain an active drug inside an outer tablet layer made of a combination of hydrophobic wax and brittle substance. This dry coating method is designed to allow for the timed release of both slow and fast release active cores by releasing the inside tablet first, then progressively disintegrating the outer shell. Lodotra™, a rheumatoid arthritis drug developed by Skye Pharma, uses this unique technology to deliver the active pharmaceutical ingredient at the most appropriate time of day to treat the disease condition[56].

EVALUATION TEST OF PULSATILE DRUG DELIVERY SYSTEM

- **Preformulation Study:** In a preformulation study, many physicochemical properties of the drug and the drug in excipient mass are evaluated[58].
- **Drug Excipients Interaction Study:** The physical and chemical interactions between the drug and the excipients can be studied using the Fourier transform infrared (FTIR) technique and differential scanning calorimetry (DSC)[59].
- **Evaluation Of Granule:** Angle of Repose, Bulk Density, Tapped Density, Carr's index (or) percent Compressibility, and Hausner's Ratio are all evaluated on the prepared granules[58].
- **Tablet Thickness:** A vernier calliper had been used to measure the thickness of the tablet. The thickness of five tablets is measured using a vernier calliper scale after they have been randomly selected from different formulations. The test is repeated for three times[58].
- **Uniformity of Weight:** On a digital weighing balance, the weight of twenty tablets was determined individually and collectively. From the total weight, the average weight of a tablet was determined. There are no more than two tablets that deviate by more than twice the percentage reported below from the average weight. The following table 4 shows the Pharmacopoeia Specification for weight variation[58]:

Table 1: Weight Uniformity Criteria for tablet

S.No.	Average weight of tablets (mg)	Percentage deviation
1	80 mg or less	±10
2	More than 80 mg but less than 250 mg	±7.5
3	250 mg or more	±5

- **Hardness/ Crushing strength:** The Monsanto Hardness tester has been used to measure the hardness or crushing strength of tablets. It's measured in kilograms per square meter. To resist mechanical shocks during manufacturing, packaging, and transportation, tablets require specific amount of strength or hardness as well as resistance to friability[58].
- **Determination Of Lag Time(t10):** The lag time in the dissolution profile increases as the % weight gain increases. The coating thickness is proportional to the increase in weight, as well as the lag time is proportional to the increase in weight. The main objective was to create a tablet that is protected from the gastric environment and releases the drug rapidly in the intestine after 5-6 hours after administration. As a result, the above batches' lag time increased from 147 to 438 mins with respect to their coating level. The lag time was determined during the dissolving test[59].

Evaluation of Polymeric Film (Only in Film Coating Approach)[59]:

a. **Visual Evaluation:** Physical properties of the film, such as whether it can be easily peeled off from the plate or not. Appearance of the film formed, such as smooth-rough surface, oily-non oily, Transparent-Opaque film

b. **Tensile Strength:** After drying, the casted films are carefully cut into film strips (length 40 mm x width 20 mm) and tensile strength is evaluated. The mechanical properties are evaluated using a guideline-based technique.

Tensile strength = Breaking Force (F)/ Cross sectional area (A)

c. **Folding endurance:** The objective of the test is to determine the efficiency of the plasticizer and the strength of the film made with different plasticizer concentrations. Folding endurance is determined by manually. A 2 × 2 cm strip of film is cut uniformly and folded at the same spot until it breaks. The value of folding endurance is determined by the number of times the film could be folded in the same spot without breaking. The test is repeated for three times.

d. **Mechanical properties:** Polymer films (6.5 X 6.7 cm2) were attached in a Teflon holder with numerous holes which was self-designed (diameter 10 mm). Films were fixed with the holder and then immersed in 0.1 N HCl for 2 hours at 37 C. (wet films). A puncture test with a Texture analyser (n = 3) is used to determine the mechanical properties of the dry and wet films. The film ruptured force–displacement curves are recorded and the following characteristics are determined using a metal probe with a hemispherical end (diameter 5 mm, length 15 cm) operated at a speed of 5 mm/min.

Puncture strength = Fmax/ ACS

Where Fmax is the maximum applied force at film break, and ACS is the cross- sectional area of the film's edge in the path of the film holder's cylindrical hole.

- **In vitro dissolution study:** The in vitro dissolution study is carried out with the help of a dissolution test which can be published in a monograph or in the standard literature. In general cases, dissolution media are 900 ml of 0.1 M HCl for 2 hours (due to the typical stomach emptying time of 2 hours) and 900 ml of phosphate buffer pH 6.8 for 3 hours) (average small intestinal transit time). After 5 hours, the dissolution medium is replaced with pH 7.4 phosphate buffer (900 ml) and the drug release is measured until the end of the hour dissolution study. A specific volume of dissolution media (1, 2, 5, 10 ml, etc.) is withdrawn at predetermined time intervals, filtered through a 0.45 m membrane filter, diluted, and assayed at wavelength maxima using a UV spectrophotometer[60].

- **Kinetic modelling of dissolution data:** To determine the kinetics of drug release, the dissolution profiles of all batches are fitted to various models such as zero order, first order, Higuchi, Hixon Crowell, Korsmeyer-Peppas[60].

- **In vivo study of prepared formulation:** The prepared formulation is evaluated in vivo to ensure that the dosage form passes through the GIT. The objective of the in vivo investigation is to determine the capsule's location as it passes through the GI system. Drug granules are substituted with barium sulphate in this investigation. The dosage form is prepared in the same way as the optimized formulation. The study uses a volunteer who has fasted overnight. The laxative is administered to the volunteer 12 hours before the start of the study to ensure that the GIT content is completely empty. At 2-h, 3-h, 5-h, and 8-h time intervals, an X-ray study is performed[60].

- **Pharmacokinetic parameters comparison:** Pharmacokinetic parameters such as Cmax (g/ml), tmax (h), AUC (ng.h/ml), and t12 (h) are compared for the optimized formulation and the marketed tablet[60].

- **Dissolution–ex vivo permeation study using everted rat intestine:** A male Wistar rat's intestine is isolated. The small intestine is removed and the lumen is carefully cleaned with a Krebs-Ringer solution after a median incision has been made into the abdomen. The distal 5 cm of the intestinal segment is everted and utilized. The isolated everted intestinal segment is mounted to a straight cannula on one end and threaded to a 1 g weight on the other. The system is completely immersed in Krebs-Ringer solution in the dissolution vessel of the dissolution test apparatus, which contains 900 mL of suitable dissolution fluid. During the investigation, the assemblies are maintained at 37± 0.5°C with a constant supply of bubbling oxygen, and aeration is assured. The drug's market samples and a manufactured optimized batch are both evaluated (n = 3). Both market samples and a manufactured optimized batch of the drug are evaluated (n = 3). The drug diffuses from the dissolution medium (mucosal side) into the serosal side (absorption compartment), after filtration through a membrane filter with a pore size of 0.45 m, and is evaluated at regular intervals using a validated analytical method[61].

CONCLUSION

Although sustained and controlled drug delivery systems have seen a lot of success and application in the field of medications, they fail to administer drugs in accordance with the circadian behaviour of diseases, for which pulsatile systems are beneficial. Pulsatile delivery methods can provide patients with improved therapeutic effects. Pulsatile drug delivery is one such technology that, by delivering a drug at the right time, right place, and right amount, holds promising benefits for patients suffering from chronic diseases such as diabetes, arthritis, asthma, hypertension, and so on. Knowledge of circadian time structure, rhythm in disease pathophysiology or 24-hour pattern in symptom intensity of chronic medical diseases, and pharmaceutical chrono pharmacology is required for the successful development of a chronotherapeutic dosage form. Significant progress has been made toward developing a PDDS that may effectively treat diseases with non-constant dose therapy.

REFERENCES

1. Prasanth V.V, Modi Mitesh P., and Mathew Sam T. Pulsatile: A tool for circadian rhythm - a review. Journal of Drug Delivery and Therapeutics 2012;2(1):58-65.
2. Gurny R, Junginger HE, Peppas N, editors. In; Pulsatile Drug Delivery: Current Application and Future Trends. Stuttgart, Germany: Wissenschefliche Verlagsgesellschaft; 1993. p. 36.
3. Pandit Vinay, Sarasija Suresh. Emerging Role of Biorhythms in Optimizing Treatment of Diseases. Indian Journal of Novel Drug delivery 2009;1(1):2-10.
4. Ritschel., W.A., Forusz, H., Chrono pharmacology: a review of drugs studies. Methods and findings in experimental and clinical pharmacology 1994;16(1):57-75.
5. Vikram S. Chhabra, Shrikant K. Tilloo, Sheelpriya R., Walde, Abhay M. Ittadwar. The essentials of chrono pharmacotherapeutics. International Journal of Pharmacy and Pharmaceutical Sciences 2012;4(3):1-8.
6. Sirisha V.N. L, Namrata M., Sruthi B., Harika I., Kiran Kumar P., Kiran Y., Kumar Rao K.Pranavi. Pulsatile Drug Delivery System-A Review. International Journal of Pharmaceutical Research and Allied Sciences 2012;1(3):13-23.
7. Sunil kamboj, G D Gupta, Jagmohan Oberoy. Matrix Tablets: An Important Tool for Oral Controlled-Release Dosage Forms. Pharmainfo net 2009;7(6):1-9.
8. Rathod Shruti. Colon Targeted Pulsatile Drug Delivery: A Review. IJPSR 2007;5(2):1-11.
9. Sharma GS, Srikanth MV, Uhumwangho MU, Phani Kumar KS and Ramana Murthy KV. Recent trends in pulsatile drug delivery systems - A review. International Journal of Drug Delivery 2010;2(3):200-212.
10. Neill MC, Rashid A, Stevens HN, GB Patent No. GB2230442, 1993.
11. Sarasija S, Hota A. Colon-specific drug delivery systems. Indian Journal of Pharmaceutical Sciences 2002;62(1):1-8.
12. Kinget R, Kalala W, Vervoort L, Mooter GV. Colonic drug targeting. Journal of Drug Targeting 1998;6(2):129-149.
13. Krögel I, Bodmeier R. Pulsatile drug release from an insoluble capsule body controlled by an erodible plug. Pharmaceutical Research 1998;15(3):474-481.
14. Krögel I, Bodmeier R. Evaluation of an enzymecontaining capsular shaped pulsatile drug delivery system. Pharmaceutical Research 1999; 16(9):1424-1429.
15. Wildind IR, Davis SS, Bakhshaee M, Stevens HNE, Sparrow RA, Brennan J. Gastrointestinal transit and systemic absorption of captopril from a pulsed release formulation. Pharmaceutical Research 1992;9(2):654-657.
16. Patrick S, Wong L, Gupta S, Stewart B. Osmotically controlled tablets. In: Rathbone M, Hadgraft J, Roberts M, editors. Modified Release Drug Delivery Technology. London: Informa Health Care; 2003. p. 113.
17. Linkwitz A, Magruder JA, Merrill S. Osmotically Driven Delivery Device with Expandable Orifice for Pulsatile Delivery Effect, US Patent No. 5318558, 1994.
18. Linkwitz A., Magruder JA, Merrill S. Osmotically Driven Delivery Device with Expandable Orifice for Pulsatile Delivery Effect, US Patent No. 522,278, 1993.
19. Balaban SM, Pike JB, Smith JP, Baile CA. Osmotically Driven Delivery Devices with Pulsatile Effect, US Patent No. 5209746, 1993.
20. Magruder PR, Barclay B, Wong PS, Theeuwes F. Composition Comprising Salbutamol, US Patent No. 4751071, 1988.
21. Magruder PR, Barclay B, Wong PS, Theeuwes F. Constant Release System with Pulsed Release, US Patent No. 4777049, 1988.
22. Magruder PR., Barclay B, Wong PS, Theeuwes F. Composition Comprising a Therapeutic Agent and a Modulating Agent. US Patent No. 4851229, 1989
23. Gazzaniga A, Iamartino P, Maffione G, Sangalli ME. Oral delayed-release system for colonic specific delivery. International Journal of Pharmaceutics 1994;108(1):77-83.
24. Poli S, Busetti C, Moro L. Oral Pharmaceutical Composition for Specific Colon Delivery. EP Patent No. 0572942, 1993.
25. Sangalli ME, Maroni A, Zema L, Busetti C, Giordano F, Gazzaniga A. In vitro and in vivo evaluation of an oral system for time and/or site-specific drug delivery. Journal of Controlled Release 2001;73(1):103-10.
26. Gazzaniga A, Sangalli ME, Giordano F. Oral chronotropic drug delivery systems: achievement of time and/or site specificity. European Journal of Pharmaceutics and Biopharmaceutics 1994;40(4):246-250.
27. Suresh S, Pathak S. Chrono therapeutics emerging role of biorhythms in optimizing drug therapy. Indian Journal of Pharmaceutical Sciences 2005;67(1):135-40.
28. Sangalli ME, Maroni A, Zema L, Busetti C, Giordano F, Gazzaniga A. In vitro and in vivo evaluation of an oral system for time and/or site-specific drug delivery. Journal of Controlled Release 2001;73(1):103-10.
29. Sunil SA, Srikanth MV, Rao NS, Uhumwangho MU, Latha K, Murthy KV. Chronotherapeutic drug delivery systems: an approach to circadian rhythms diseases. Current Drug Delivery 2011;8(6):622-33.
30. Conte U, Colombo P, Manna A, Gazzaniga A. A new ibuprofen pulsed release oral dosage form. Drug Development and Industrial Pharmacy 1989;15(14- 16):2583-2596.
31. Conte U, Manna A, Colombo P. Tablet for Pharmaceutical Use Able to Release Active Substances at Successive Times, US Patent No. 4865849, 1989.
32. Krögel I, Bodmeier R. Floating or pulsatile drug delivery systems based on coated effervescent cores. International Journal of Pharmaceutics 1999;187(2):75-184.
33. Ueda Y, Hata T, Yamaguchi H, Ueda S, Kotani M. Time Controlled Explosion System and Process for Preparation for the Same, US Patent No. 4871549, 1989.
34. Ueda Y, Hata T, Yamaguchi H, Kotani M, Ueda S. Development of a novel drug release system, time-controlled explosion system (TES), Part 1: concept and design. Journal of Drug Targeting 1994;2(1):35-44.
35. Ueda S, Yamaguchi H, Kotani M, Kimura S, Tokunaga Y, Kagayama A, Hata T. Development of a novel drug release system, time-controlled explosion system (TES), Part II: design of multiparticulate TES and in vitro drug release properties. Chemical and Pharmaceutical Bulletin 1994;42(2):359- 363.
36. Amidon GL, Leesman GD. Pulsatile Drug Delivery System, US Patent No. 5229131, 1993.
37. Bodmeier R, Guo X, Sarabia RE, Skultety P. The influence of buffer species and strength on diltiazem HCl release from beads coated with aqueous cationic polymer dispersions, Eudragit RS, RL 30D. Pharmaceutical Research 1996; 13(1):52-56.
38. T Y Fan, S L Wei, W W Yan, D B Chen, J Li. An investigation of pulsatile release tablets with ethylcellulose and Eudragit L as film coating materials and cross-linked polyvinylpyrrolidone in the core tablets. Journal of Controlled Release 2001;77(3):245-251.
39. Survase S, Kumar N. Pulsatile drug delivery: Current Scenario. Current Research in Pharmaceutical Sciences 2007;8(2):27-33.

40. Y.H. Bae, T. Okano, S.W. Kim. 'On–off' thermocontrol of solute transport. I. Temperature dependence of swelling of N-isopropylacrylamide networks modified with hydrophobic components in water. Pharmaceutical Research 1991;8(4):531–537.

41. Y.H. Bae, T. Okano, S.W. Kim. 'On–off' thermocontrol of solute transport. II. Solute release from thermosensitive hydrogels. Pharmaceutical Research 1991;8(5):624–628.

42. K. Kataoka, A. Harada, Y. Nagasaki. Block copolymer micelles for drug delivery: design, characterization and biological significance. Advanced Drug Delivery Reviews 2001;47(1):113–131.

43. K. Ishihara, M. Kobayashi, I. Shinohara. Control of insulin permeation through a polymer membrane with responsive function for glucose. Makromolekulare Chemie Rapid Communication 1983;4(3):327–331.

44. N. Yui, T. Okano, Y. Sakurai. Inflammation responsive degradation of crosslinked hyaluronic acid gels. Journal of Controlled Release 1992;22(2):105–116.

45. N. Yui, J. Nihira, T. Okano, Y. Sakurai. Photo-responsive degradation of heterogeneous hydrogels comprising crosslinked hyaluronic acid and lipid microspheres for temporal drug delivery. Journal of Controlled Release 1993;26(2):141– 145.

46. T. Miyata, N. Asami, T. Uragami. Preparation of an antigen sensitive hydrogel using antigen–antibody bindings. Macro molecules 1999;32(6):2082–2084.

47. R. Kishi, M. Hara, K. Sawahata, Y. Osada. Conversion of chemical into mechanical energy by synthetic polymer gels (chemo mechanical system). Polymer Gels — Fundamentals and Biomedical Applications, Plenum Press, New York, 1991, pp. 205–220.

48. I.C. Kwon, Y.H. Bae, T. Okano, B. Berner, S.W. Kim. Stimuli sensitive polymers for drug delivery systems. Makromolekulare Chemie Macromolecular Symposia 1990;33(1):265–277.

49. Sharma S and Pawar A. Low Density multiparticulate system for pulsatile release of meloxicam. International Journal of pharmaceutics 2006;313(1):150-158.

50. Singh D. K., Poddar A.S., Nigade S.U., Poddar S. S: Pulsatile Drug Delivery System: An Overview. International Journal of Current Pharmaceutical Review and Research 2011; 2(2):55-80.

51. Singh Anamika, Dubey Harikesh, and Shukla Indu, Singh Dharmchand P: Pulsatile Drug Delivery System: An Approach of Medication according to Circadian Rhythm. Journal of Applied Pharmaceutical Science 2012;2(3):166-176.

52. Ms. Shah Radhika, Ms. Doshi Nidhi, Dr. Patel M. R., Dr. Patel K. R.: Pulsatile Drug Delivery: A Review. Internationale Pharmaceutica Sciencia 2012;2(2):45-52.

53. Moturi Vihar, Khan Arshad Bashir: Chronotherapeutics in Development of Pulsatile Delivery Systems. International Journal of Pharmaceutical Sciences and Research 2012; 3(11):4086-4095.

54. Reddy Ravi Kumar J. C. Madhu Sudhana Chetty: Review on: Pulsatile Drug Delivery Systems. Journal 0f Pharmaceutical Sciences and Research 2009;1(4):109-115.

55. Bauskar Mohit D, Nandedkar S.Y, Wagh Rajendra D: Formulation design and optimization of pulsatile release tablet of acebrophlline with swelling and erodible layers for treatment of nocturnal bronchial asthma. International. Journal Pharmaceutical Science and Research 2011;2(12):3100-3108.

56. Patel Vipul P, Soniwala Moinuddin M: Pulsatile Drug Delivery System for Treatment of Various Inflammatory Disorders-A Review. International Journal of Drug Development and Research 2012;4(3):67-87.

57. Bauskar Mohit D, Nandedkar S.Y, Wagh Rajendra D: Formulation design and optimization of pulsatile release tablet of acebrophlline with swelling and erodible layers for treatment of nocturnal bronchial asthma. International. Journal Pharmaceutical Science and Research 2011;2(12):3100-3108.

58. Lachman "The theory and Practice of Industrial Pharmacy" 3rd edition.

59. Ahmad Mohamad, Andrei Dashevsky. pH-independent pulsatile drug delivery system based on hard gelatin capsules and coated with aqueous dispersion Aquacoat ECD. European Journal of Pharmaceutics and Biopharmaceutics 2006;64(2):173-179.

60. Dasharath M Patel, Rushiraj H Jani, Chhagan N Patel. Design and evaluation of colon targeted modified pulsincap delivery of 5-fluorouracil according to circadian rhythm. International Journal of Pharmaceutical Investigation 2011;1(3):172-181.

61. Mariappan TT, Singh S. Evidence of efflux mediated and saturable absorption of rifampicin in rat intestine using the ligated loop and everted gut sac technique. Molecular Pharmaceutics. 2004;1(5): 363–367.

Source of Support: The author(s) received no financial support for the research, authorship, and/or publication of this article.

Conflict of Interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.