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Pulsatile Drug Delivery System

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Abstract

Pulsatile Drug Delivery Systems are gaining a lot of interest as they deliver the drug at the right place at the right time and in the right amount, thus providing spatial, temporal and smart delivery and increasing patient compliance. These systems are designed according to the biological rhythm of the body. Here drug delivery is facilitated according to disease rhythm. The principle rationale for the use of pulsatile release of the drugs is where a constant drug release is not desired. As put to has been designed in such a way that a complete and rapid drug release is achieved after the lag time. Various systems like capsular systems, osmotic systems, single and multiple-unit systems based on the use of soluble or erodible polymer coating and use of rupturable membranes have been dealt with in the article.

These systems are beneficial for the drugs having chrono pharmacological behavior such as drug used in treatment of rheumatoid arthritis, osteo arthritis and ankylosing spondylitis like inflammatory disorders. Current review article discussed the reasons for development of pulsatile drug delivery system, types of the disease in which pulsatile release is required, classification, advantages, and limitation, of pulsatile drug delivery system.

Keywords: *Pulsatile drug release, lag time, circadian rhythm.*

INTRODUCTION

With the advancement of the technologies in the pharmaceutical field, drug delivery systems have drawn an increasing interest over the last few decades. Nowadays, the emphasis of

pharmaceutical galenic research is turned towards the development of more efficacious drug delivery systems with already existing molecule rather going for new drug discovery because of the inherent hurdles posed in drug discovery and development Process [(1).]

The drug delivery has typically intended for predicting the absorption from an straightforward chemical form either from the stomach or the injection site a control release pattern shows a difficult type of drug release fig 1 in which drug concentration is maintained in the therapeutic window for a prolonged period (Sustained release they're by ensuring a sustained release of action[(2).]

Pulsatile drug delivery is defined as the rapid and transient release of certain amount of active molecules within a short time period immediately after a predetermined off released period, i.e., lag time, or 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. Such a release pattern is known as pulsatile release.

To introduce the concept of chronotherapeutic, it is important to define the following concepts [(3)]

Chronobiology

Chronobiology is the science concerned with the biological mechanism of the diseases according to a time structure. “Chrono” pertains to time and “biology” pertains to the study, or science, of life.

Chrono pharmacology

Chrono pharmacology is the science concerned with the variations in the pharmacological actions of various drugs over a period of time of the day.

Chrono pharmacokinetic

Chronopharmacokinetic involves study of temporal changes in drug absorption, distribution, metabolism and excretion. Pharmacokinetic parameters, which are conventionally considered to be constant in time physiological functions displaying circadian rhythm (CR). 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.

Chronotherapy

Co-ordination of biological rhythms and medical treatment is called chronotherapy.

Chronotherapeutic

Chronotherapeutic is the 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 that patients take their medication may be even more significant than was recognized in the past.

Pulsatile systems are made such that the medication is accessible at the site of action at the right time in the right amount. These techniques are advantageous for drugs that have the first-pass effect, a medication used to treat aliments following Chrono pharmacological behavior drugs having specific absorption sites in GIT, targeting to; and cases where night-time dosing is required.

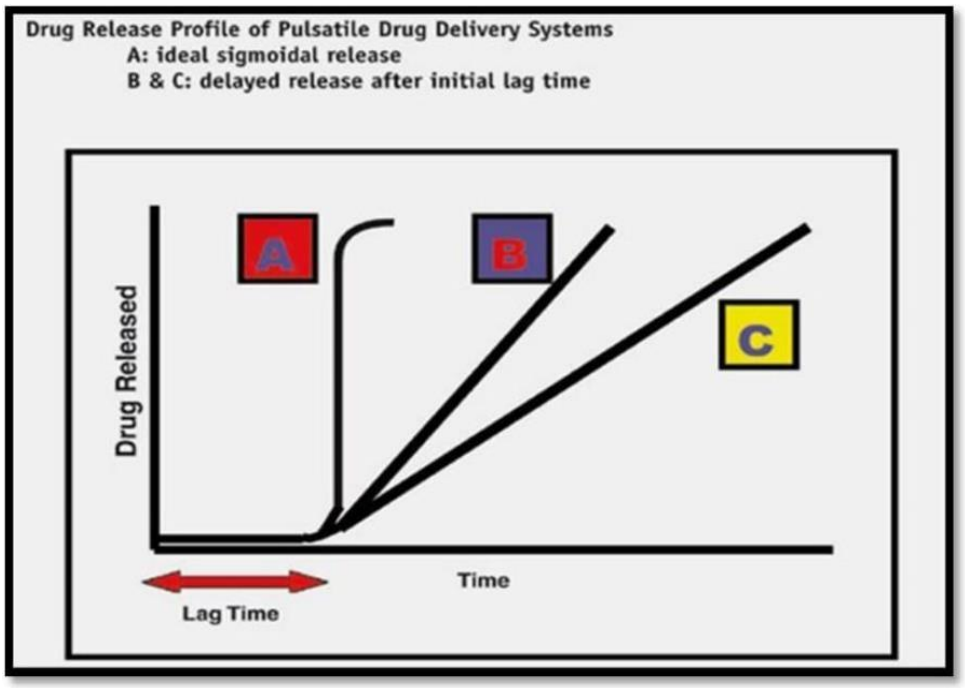

Fig1: Drug release profile of pulsatile drug delivery sysytems

Advantages

Gastric residency time that is predictable, repeatable, and brief there is less diversity between and among individuals.

1. There is a low risk of local irritation.
2. Improved Patient comfort and compliance
3. Extended daytime or nighttime activity
4. Drug loss is prevented by extensive first pass metabolism [(4)].
5. Flexibility in design
6. Improve stability [(1)].
7. It decreases food effect when the drug is given with food
8. The release of the drug in this system is not affected by the change in pH of the GI Tract, the viscosity of lumen contents, and the agitation rate of the GI Tract.
9. This system can be used in different solid dosage forms, such as microspheres, granules, tablets, pallets, capsules, etc [(5)].
10. 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
11. Reduces drug dosage without reducing therapeutic effects
12. Due to lower cytochrome P450 isoenzymes, drug interactions are reduced.
13. Multiple dosing in a single dosage form is possible with pulse release [(6)].
14. Lower daily cost to patient due to fewer dosage units are required by the patient in therapy.
15. Drug adapts to suit circadian rhythms of body functions or diseases.
16. Protection of mucosa from irritating drugs [(7)].

Disadvantages

1. Lack of manufacturing reproducibility and efficacy
2. Multiple formulation steps
3. Higher cost of production [(1)].
4. Need of advanced technology [(3)]
5. Drug load is low [(6)].
6. In-vivo variability in single unit pulsatile drug delivery system [(7)].
7. Trained/skilled personal needed for manufacturing [(8)].

Need of Novel pulsatile drug delivery system

1. Numerous body functions follow circadian rhythm, i.e., their action increases or decreases with time. Numerous hormones in the body prove daily in addition to timely fluctuations of their blood ranges. Circadian outcomes are also experiential in case of pH and acid secretion in gastric emptying, stomach and GI blood transfusion [(8)].
2. Acid secretion in the stomach, gastrointestinal blood transfusion, Gastric emptying and cholesterol synthesis follows circadian rhythm [(5)].
3. Lag time is important for the ones tablets go through acidic degradation that worsen the gastric mucosa or results in nausea and vomiting [(8)].
4. Disease like asthma, myocardial infarction, angina pectoris, rheumatic disease, ulcer, and hypertension follows circadian rhythm [(5)].
5. Targeting a drug to distal organs of GIT like the colon the drug release ought to be prohibited in the upper two-1/3 portion of the GIT [(8)].
6. Drug which undergo degradation in gastric acidic medium, example, peptides drugs[(5)].
7. Drugs create biological lenience due to incessant exposure of drugs in the body. This system lenience by giving insulates time[(8)]
8. Drugs that shows extensive first pass metabolism[(5)]

Diseases Requiring Pulsatile drug Delivery

Thorough understanding of the disease physiology is required before designing the pulsatile drug delivery system. Diseases where rhythmic circadian organization of the body plays an important role, pharmacokinetics and/or pharmacodynamics of the drugs is not constant within 24 h. Table .1. enumerates various diseases showing such a chronological behavior (9).

Many of our body functions like metabolism, sleep patterns, behaviour, physiology and hormone production are regulated by circadian rhythm. Capillary resistance and vascular reactivity are higher in the morning and decrease in the day later on. Circadian changes are observed in normal lung functioning, which is very low in early morning hours. Also, Blood pressure is found to be high in the morning and low during night. Rheumatoid arthritis patients suffer more pain in the morning period while osteo- arthritis patients feel more pain in the night time. In all such diseases, pulsatile drug delivery can be immensely beneficial (10).

Table 1. Diseases that require pulsatile drug delivery

Disease	Chronological behaviour	Drugs used
Peptic ulcer	Acid secretion is high in theafternoon and at night	H2 blockers
Asthma	Precipitation of attacks during night or at early morning hour	B2 agonist, Antihistaminics
Cardiovascular diseases	Cardiovascular diseases BP is at its lowest during the sleep cycle and rises steeply during the early morning awakening period Nitroglycerin, Calcium channel blocker, ACE inhibitors, β Blockers etc.	Nitroglycerin, Calcium channel blocker, ACE inhibitors, β Blockers etc.
Arthritis	Arthritis Pain in the morning and more pain at night NSAIDs, Glucocorticoids	NSAIDs, Glucocorticoids
Diabetes mellitus	Increase in the blood sugar level after meal	Sulfonylurea, Insulin, Biguanide
Attention deficit	syndrome Increase in DOPA level in afternoon	Methylphenidate
Hypercholesterolemia	Cholesterol synthesis is generally higher during night than during day time	HMG CoA reductase inhibitors
Allergic rhinitis	Worse in the morning/upon rising	Antihistaminics
Hormone secretion	Growth hormone and melatonin are produced at night testosterone and	Corticosteroids

	cortisol in morning hr	
Angina Pectoris	Angina Pectoris Chest pain and ECG changes more common in the early morning Antianginal drugs	Antianginal drugs
Myocardial Infraction	Incidence higher in the early morning Cardiovascular agents Stroke Incidence higher in the morning	Cardiovascular agents
Cancer	The blood flow to tumors is threefold greater during each	Vinca alkaloids, Taxanes
	daily activity phase of the circadian cycle than during the daily rest phase.	
Duodenal ulcer	Duodenal ulcer Gastric acid secretion is highest at night, while gastric and small bowel motility and gastric emptying are all slower at night.	Proton pump inhibitor

Mechanism of drug release from pulsatile drug delivery system [(11)]

The mechanism of drug release from PDDS can be occurring in the following ways:

Diffusion

On contact with aqueous fluids in the gastrointestinal tract (GIT), water diffuses into the interior of the particle. Drug dissolution occurs and the drug solutions diffuse across the release coat to the exterior.

Erosion

Some coatings can be designed to erode gradually with time, thereby releasing the drug contained within the particle. Osmosis In allowing water to enter under the right circumstances, an osmotic pressure can be built up within the interior of the particle. The drug is forced out of the particle into the exterior through the coating.

Methods used for PDDS (12)

- Time controlled
- Stimuli induced
- External regulated

Time-controlled PDDS

Single-unit pulsatile system

1. Based on Capsule type (Pulsincap System type)
2. Based on a Capsular system with Osmosis type

- PORT System
- Expandable orifice System
- Pulsatile drug delivery by solubility modulation
- Delivery by series of stops

3. Pulsatile system contains erodible/ soluble barrier coatings Compressed tablets, Multilayered tablets, Time clock Systems, Chronotropic Systems.
4. Pulsatile systems with rupturable coating

Multi-particulate / Multiple unit systems

- Pulsatile system with a rupturable coating
- Rupturable coating by Osmotic system
- Pulsatile Delivery by modifications in the Membrane Permeability

Stimuli Induced

1. Temperature-induced type
2. Chemical-induced stimuli type

a) Glucose-responsive insulin release
b) Inflammation-induced

c) Release of drug from intelligent gels responding to antibody concentration
d) Electrical stimuli responsive pulsatile
e) pH-sensitive type of drug delivery

External Regulated

1. Electro responsive to drug release
2. Stimulation by ultrasonically method
3. Stimulation by the magnetically induced method

Time-controlled PDDS

Single Unit Pulsatile Systems: The single-unit systems show the release of drugs based on the capsule type of system [(12)].

Capsular Systems

Single-unit systems are mostly urbanized in capsule form. The insulate time is managed by a plug, pushed away by erosion or swelling, and the drug is launched as a Pulse from the insoluble pill frame. For e.g., Pulsincap gadget is one such system that comprises a water-insoluble tablet enclosing the drug reservoir. A swellable hydrogel plug was used to seal the drug substances into the tablet body . When this tablet got here in contact with the GI fluid or dissolution fluid, it swelled, and after a lag, the plug drove itself outside the pill and rapidly released the drug [(8)].

Polymers used for the process of designing hydrogel plug-like swellable polymers but Insoluble and permeable nature (ex: Polymethacrylates), Compressed erodible polymer nature (ex: HPMC, PVA, PEO), Congealed melted polymer nature (ex: glyceryl monooleate), Enzymatic Erodible polymer nature (ex: Pectin) (12).

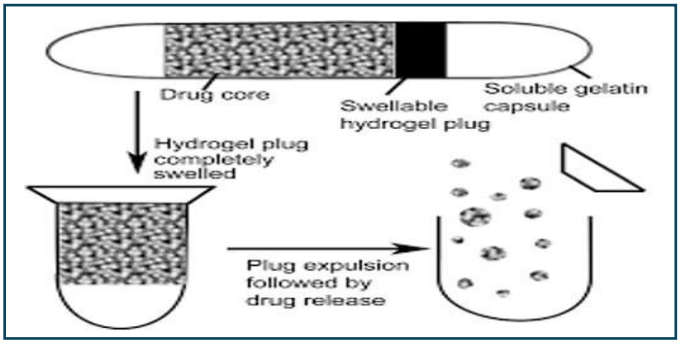

Fig 2: Schematic design of Pulsincap system

Capsule Systems with Osmosis Type

PORT System: It consists of a capsule with a semipermeable coating membrane. The insoluble plug is inside the capsule body and contains an insoluble plug along with an osmotically active agent and drug formulation. When the capsule's contact with the dissolution fluid, water can enter through the coated semipermeable membrane, creating pressure. The insoluble plug was expelled after the lag time and helps to avoid the second dose type [12].

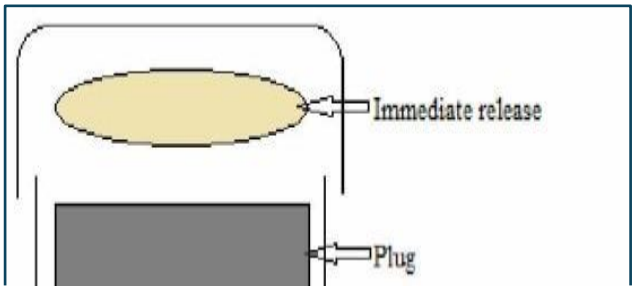

Fig 3: Schematic design of osmotic system

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 layer16. 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 [6].

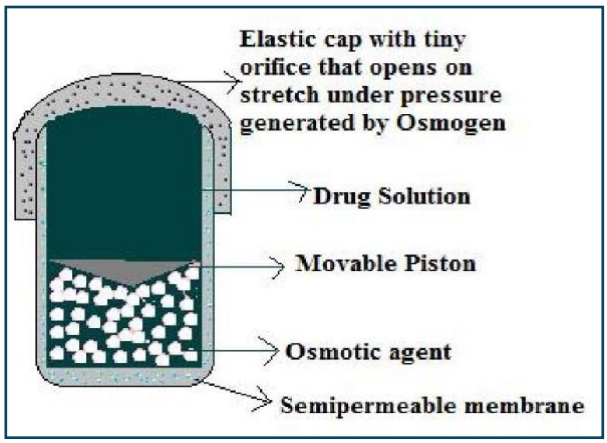

Fig 4: System based on expandable orifice

Delivery by solubility modulation

A solubility modulator is present for pulsed delivery of a variety of drugs in these systems. The system was especially developed for the delivery of salbutamol sulphate. The compositions consist of a drug (salbutamol sulphate) along with a modulating agent (sodium chloride). The amount of NaCl was less than that required to maintain saturation in a fluid entering the osmotic device. Pulsed delivery depends on the 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. These values show that the solubility of a drug is a function of the modulator's concentration, while the modulator's solubility is largely independent of drug concentration. The modulating agent can be a solid organic acid, inorganic acid or organic salt [(10)].

Delivery by a 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. The number of stops and the longitudinal placements of the stops along the length of the capsule dictate the number and frequency of the pulses, and the configuration of the partition controls the pulse intensity. This system was used to deliver porcine somatotropin [(1)].

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 quickly from reservoir core. The lag time depends on the thickness of the coating layer [(4)].

The chronotropic system

The Chronotropic® system consists of a drug containing core coated by hydrophilic swellable hydroxypropylmethyl cellulose (HPMC),that is responsible for a lag phase in the onset of release. Additionally, 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.

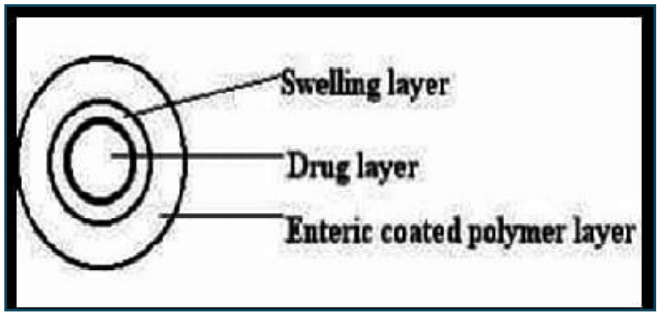

Fig 5: Chronotropic system

The lag time is controlled by the thickness and the viscosity grades of HPMC. Both in-vitro and in vivo lag times correlate well with the applied amount of the hydrophilic retardin polymer. The system is suitable for both tablets and capsules.

'TIME CLOCK' System

The lag time could be controlled by varying the thickness of the film. After the lag time, i.e., the time required for rehydration, the core immediately releases the drug. This system has shown reproducible results in vitro and in vivo. The effect of low calorie and high calorie meal on the lag time was studied using gamma scintigraphy.The mean lag time of drug release was 345 and 333 min respectively.

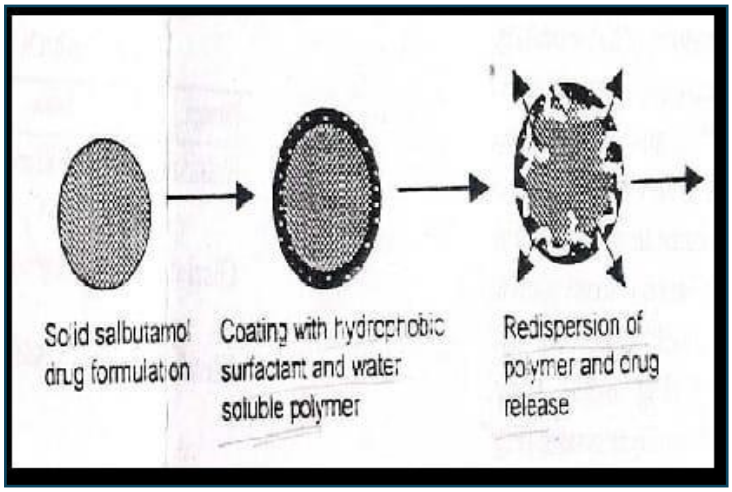

Fig 6: Time clock system

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. Press-coated

Pulsatile drug delivery systems

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

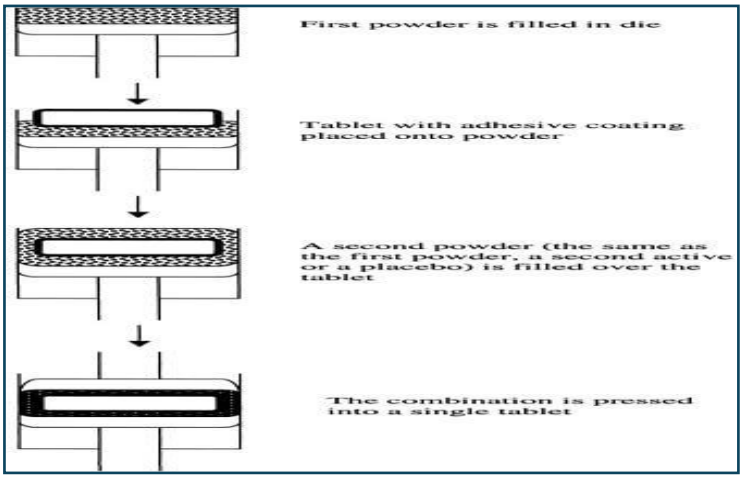

Fig 7: Press- coating technique

Multilayered Tablets

A delivery design with two pulses was gotten from a three-layered tablet containing two medication-containing layers separated by a medication-free gellable polymeric hindrance layer. 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. The rate of gelling or dissolution of the barrier layer control the appearance of the second pulse. The gelling polymers reported include cellulose derivatives like HPMC, methyl cellulose, or polyvinyl alcohols of various molecular weights and the coating materials include ethyl cellulose, cellulose-acetate propionate, methacrylic polymers, acrylic and mehtacrylic co-polymers, and polyalcohols.

Multi-particulate/Multiple Unit Type Systems

Pulsatile System with Erodible or Soluble Barrier Coatings

The number of PDDS systems are present in the form of reservoir type systems with a barrier layer so the used barrier is soluble, erodible in nature after a specific lag time period so the drug release rapidly from the system of drug containing reservoir core. So, the lag time period is completely depending on the coating layer thickness. In Chronotropic system drug core (In Tablets and capsules) is coated by hydrophilic swellable polymers. Conversely the lag time period is depending on the layer thickness and Viscosity of polymer grades. In compressed tablet system, the direct compression technique is used to compress coating of both the core and coat. The outer compressed coated tablet shows the initial dose with fast disintegration and the inner compressed layer consists of insoluble components in the gastric media but soluble drug, release in the intestine in multilayer tablet system [(12)].

Pulsatile Systems with Rupturable Coating

Comparable to a single-unit system, the rupturing outcome is achieved by coating the individual units with effervescent (or) swelling agents. Drug transport was controlled by the break of the membrane.

The timing of discharge was controlled by the thickness of the coating and the quantity of H2O soluble polymer to achieve the pulsed release .The swelling agent includes superdisintegrants like sodium starch glycollate, carboxymethylcellulose, L-hydroxy propyl cellulose, and sodium starch glycollate. Polymers like polyethylene glycol, polyacrylic acid, etc. are a mixture of tartaric acid & sodium bicarbonate that are used as effervescent agent [(8)].

Rupturable Coating by Osmotic-Based Systems

It consists of a combination of both osmotic and swelling agent effects. The drug, low bulk density containing lipid substance and disintegrating agent present in the core and finally coated with cellulose acetate polymer. So, the drug core is in contact with the aq. media water penetrate into the drug core and displacing the lipid substance. The lipid material depletion leads to an increase in the internal pressure until it reaches critical stress and it shows the rupturing of the coating [12].

Stimuli-induced Pulsatile Release System

Stimuli-based drug delivery systems discharge the drug in rejoinder to stimuli precipitated by the organic surroundings. Discharge of the drug in rejoinder to those systems results from stimuli-induced modifies in the micelles or in the gels, which may deswell, erode or swell in response to the particular stimuli. The drug is released after inspiration by any biological factor, like temperature or other chemical stimuli. These schemes are considered brilliant delivery candidates since they can be modified according to the job to be achieved [8].

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. Y.H. Bae et al developed indomethacin pulsatile release pattern in the temperature ranges between 200C and 300C by using reversible swelling properties of copolymers of N-isopropyl acrylamide and butyrylacrylamide (13).
Chemical stimuli induced pulsatile systems [14]

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.

Inflammation induced pulsatile release device

On receiving any physical or chemical stress, such as injury, fracture etc., inflammation take place at the injured sites. During inflammation, hydroxyl radicals are produced from these inflammation- responsive cells. Yui and co-workers focused on the inflammatory- induced hydroxyl radicals and designed drug delivery systems, which responded to the hydroxyl radicals and degraded in a limited manner. They used hyaluronic acid (HA) which is specifically degraded by the hyaluronidase or free 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, it is possible to treat patients with inflammatory diseases like rheumatoid arthritis; using anti-inflammatory drug incorporated HA gels as new implantable drug delivery systems.

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.

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.

External Regulated Pulsatile Drug Delivery

In which the release of the drug can be externally regulated by ultrasound, electrical, magnetic and irradiation (light) stimuli. In a magnetic regulated system, magnetic beads are placed in the implant so the drug release occurs from the magnetic field application. In an ultrasound system, the ultrasonic waves show erosion of the polymer matrix. In the Irradiation method, irradiation of light rays is used for drug release, and the light irradiation light rays desire the pattern of drug release by drug exposed to light. In Electric induced system, the presence of both electro and pH-sensitive responsive systems causes drug release [(12)].

EVALUATION TEST OF PULSATILE DRUG DELIVERY SYSTEM [(6)]

1. Preformulation Study

In a preformulation study, many physicochemical properties of the drug and the drug in excipient mass are evaluated.

2. 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).

3. 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.

4. 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.

5. 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 2 shows the Pharmacopoeia Specification for weight variation.

Table 2: Weight Uniformity Criteria for tablet

Sr.no.	Average weight of tablets (mg)	Percent 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.

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.

Evaluation of Polymeric Film (Only in Film Coating Approach)

6. 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

7. 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)

8. 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.

9. 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 (diameter5 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.

10. 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 spectrophotometer60.

11. 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.

12. 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.

13. 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.

14. 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.

Marketed Technologies of Pulsatile Drug Delivery

Different marketed technologies has been developed for pulsa-tile drug delivery as PulsincapTM, Diffucap®, Three dimentional prininting®, CODAS®, OROS®, IPDAS®, GEOCLOCK®, Ritalina®, Uniphyl®, Opana®ER.48-50 Some of them are discussed below[(15)].

Pulsincap™ technology

Pulsincap was created by R.R. Scherer International Corporation (Michigan). This gadget comprises a non-breaking down half case body fixed at the open end with a hydrogel plug that is covered by a water-dissolvable cap. The entire unit is covered with an enteric polymer to keep away from the issue of variable gastric emptying. At the point when this capsule interacts with the dissolution fluid, it swells, and after a lag time, the attachment propels itself outside the case and quickly delivers the medication. Another definition approach was as bead or granule with a four-layered round structure, which comprises a core, a medication swelling agent (e.g., sodium starch glycolate or carboxymethyl cellulose sodium), and an external film of water-insoluble polymer (e.g., ethylcellulose and Eudragit® RL). The entrance of GI liquids through the external film causes the extension of the swelling agent. The subsequent pressure because of expanding power prompts the obliteration of the film and ensuring fast medication discharge. Polymers utilized for planning the hydrogel plug were different thickness evaluations of hydroxyl propyl methyl cellulose, polymethyl methacrylates, polyvinyl acetic acid derivation, and polyethylene oxide. Another new methodology was

enteric-covered, coordinated delivery, and press- covered tablets (ETP tablets). These tablets were created by coated enteric polymer on coordinated delivered, press-coated tablets made out of an external shell of hydroxyl propyl cellulose and core tablets containing diltiazem hydrochloride as a model medication [16].

Patel and Patel developed a modified Pulsincap device containing Diclofenac Sodium to target the drug in the colon. This is a site specific and time dependent formulation i.e., by administering the formulation at bed time, symptoms that are experienced early in the morning are avoided. This therapeutic effect is prolonged by continuously releasing the medication over an extended period of time after administering a single dose. The objective of the study was to explore the time-and pH-dependent controlled drug delivery of Diclofenac Sodium using the pulsincap system [15].

Diffucaps® technology

A unit dosage form, such as a capsule is used for delivering drugs into the body in a circadian release fashion. DIFFUCAPS® is a multiparticulate technology by Reliant Pharmaceuticals LLC, for a chronotherapeutic delivery of a combination of two drugs, Verapamil HCl and Propanolol HCl, as an extended release tablet (Innopran®). Pulsincap® system is one of the most used pulsatile systems based on capsules. It was developed by R. P. Scherer International Corporation, Michigan, US. Diffucaps®, and comprises of one or more populations of drug-containing particles (beads, pellets, granules, etc.). Each bead population exhibits a pre-designed rapid or sustained release profile, with or without a predetermined lag time of 3 – 5 hours. The active core of the dosage form may comprise of an inert particle or an acidic or alkaline buffer crystal (e.g., cellulose ethers), which is coated with an API-containing film-forming formulation and preferably a water-soluble film forming composition (e.g., hydroxypropylmethylcellulose, polyvinylpyrrolidone) to form a water-soluble / dispersible particle. The active core may be prepared by granulating and milling and / or by extrusion and spheronization of a polymer composition containing the API. Such a ChrDDS is designed to provide a plasma concentration time profile, which varies according to the physiological need during the day that is, mimicking the circadian rhythm and severity / manifestation of a cardiovascular disease, predicted based on pharmacokinetic and pharmacodynamic considerations and In vitro / in vivo correlations. This technology has been

used to formulate the first and recently FDA approved propranolol containing ChrDDS (InnopranRXL) for the management of hypertension [3].

3DP®

3DP is a novel strong freestyle creation innovation that has been applied to the manufacture of complex drug gadgets, or 3DP is fast prototyping (RP) innovation. Prototyping includes developing explicit layers that utilization powder handling and fluid restricting materials. Reports in the writing have featured the numerous benefits of the 3DP framework over different cycles in upgrading drug applications; these remember new techniques for the plan, improvement, production, and commercialization of different kinds of strong measurement structures. For instance, 3DP innovation is adaptable in that it very well may be utilized in applications connected to straight medication conveyance frameworks, colon-focused on conveyance frameworks, oral quick crumbling delivery system, drifting conveyance frameworks, time-controlled, and beat discharge delivery system just as dose structures with multiphase delivery properties and implantable DDS. Likewise, 3DP can give answers for settling challenges identifying with the conveyance of ineffectively water-dissolvable medications, peptides and proteins, profoundly harmful and strong medications, and controlled arrival of multi drugs in a solitary measurement structure. Because of its adaptable and exceptionally reproducible assembling measure, 3DP has a few benefits over customary packing and other RP innovations in manufacturing strong DDS. This empowers 3DP to be additionally produced for use in pharmaceutics applications. Be that as it may, a few issues limit the further uses of the framework, for example, the choice of reasonable excipients and the drug store specialized properties of 3DP items. Further improvements are thusly expected to defeat these issues so 3DP frameworks can be effectively joined with regular pharmaceutics [16].

Limitations of the technology as relating to pharmaceuticals have been addressed and prototype dosage forms have been fabricated. The resolution of the 3DP tablets was found to depend on particle size and liquid migration during printing and drying. The surface finish of 3DP tablets was enhanced by uniaxial pressing. Migration inhibiting additives were effective in limiting transport. Both aqueous and ethanol-based solutions showed a decrease in migration on the order of 20% when appropriate powder bed additives were introduced. Migration was also decreased by pre-printing barriers to confine secondary printed drug

solutions. Low dosage forms were fabricated with as little as 2.3 nanograms. Lower dosages are expected upon dilution of the initial drug solution. Printing forms with high dosage is limited by powder void volume, filling efficiency and drug solubility limits.

Complex oral dosage forms were fabricated with 3DP to show lagged-release, extended-release, double-release and zero-order-release. Release properties, such as lag time and release rate, were manipulated by varying the printing parameters. Dual-release and zero- order-release forms were fabricated using a surface degradation/erosion system based on HPMC, lactose and Eudragit RL100. Erosion rate constants were used to model release from tablets with non-uniform drug distributions. Diclofenac and chlorpheniramine dual- release tablets were designed with 3 drug regions and dissolution of the tablets followed the model closely, exhibiting 2 onsets.

Two types of zero-order tablets were invented and fabricated by 3DP. These contained drug concentration gradients designed to complement the volumetric non-uniformity of eroding shells. Three formulations showed constant release of diclofenac sodium over 1–7 h (9.6 mg/hr), 1–15 h (6.8 mg/hr) and 1–36 h (2.5 mg/hr) (15).

CODAS®

In specific cases, the quick arrival of medications is bothersome. A deferral of medication activity might be needed for an assortment of reasons. Chronotherapy is an illustration of when medication delivery might be modified to happen after a delayed stretch after organization. Energy Drug Technology created CODAS® innovation to accomplish this drawn-out stretch. The numerous benefits of the CODAS® innovation incorporate a delivery profile intended to commend circadian example, controlled beginning, an all-inclusive delivery conveyance framework, pace of delivery autonomous of pH, stance, and food, “sprinkle” dosing by opening the case and sprinkling the substance on food, decrease in the viable day by day portion and medication openness, GI plot focusing for neighbor-hood impact, and diminished foundational openness to accomplish an objective profile [(16)].

Verelan® PM utilizes the restrictive CODAS™ innovation, which is intended for sleep time dosing, consolidating a 4–5 h delay in drug conveyance. The controlled-beginning delivery system brings about a most extreme plasma focus (Cmax) of verapamil in the first part of the

day hours. These pellet-filled containers accommodate broadened arrival of the medication in the GI lot. The Verelan® PM plan has been intended to start the arrival of verapamil 4–5 h after ingestion. This postponement is presented by the degree of non- enteric delivery controlling polymer applied to tranquilize stacked globules. The delivery controlling polymer is a blend of water-solvent and water-insoluble polymers. As water from the GI lot comes into contact with the polymer-covered globules, the water-solvent polymer gradually breaks up, and the medication diffuses through the subsequent pores in the covering. The water-insoluble polymer keeps on going about as an obstruction, keeping up the controlled arrival of the medication. The pace of delivery is free of pH, stance, and food. Multiparticulate systems, such as Verelan® PM, are free of GI motility [(15)].

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 an 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 the other, a cosmetically active agent. Upon contact with the GI fluid this osmotic agent changes its characteristic from a non-dispensable to a dispensable viscosity. As a result the active pharmaceutical is pushed away through the channel due to the pump effect of the osmotic agent. It is generally used in the designing of an extended release tablet [(3)].

IPDAS®

The IPDAS is another oral medication conveyance approach that applies to GI aggravation drugs, including the nonsteroidal mitigating drug (NSAID) class. IPDAS® conveyance framework can likewise be utilized to present the benefits of multiparticulate innovation in a tablet dose structure. The IPDAS® innovation is made out of various high-thicknesses, controlled-discharge dots, which are compacted into a tablet structure. When an IPDAS® tablet is ingested, it deteriorates and scatters globules containing a medication in the stomach, which hence passes into the duodenum and along with the GI parcel in a controlled and continuous way, autonomous of the taking care of the state. The arrival of dynamic fixing is constrained by the polymer system used to cover the dots or potentially the miniature lattice of polymer/dynamic fixing shaped in the expelled/spheronized multiparticulates [(16)].

The intestinal insurance of IPDAS® innovation is characteristic of the multiparticulate idea of the definition, which guarantees a wide scattering of aggravation drugs all through the GI lot. IPDAS® was at first planned as a feature of the advancement interaction for Elan Drug Technologies' exclusive naproxen definition, Naprelan®.

Even though naproxen, as the free corrosive or the sodium salt has pharmacokinetic qualities that are predictable with once-day-by-day dosing, the GI aggravation and ulcer genic potential are related with a huge bolus portion of naproxen blocks safe utilization of a prompt delivery structure. In addition, the ideal pharmacodynamic action of a once-day- by-day measurement type of naproxen requires quickly accessible naproxen for a brief beginning of pain-relieving movement just as a delayed period of retention to give 24 h pain relieving/calming action. The goal was to build up a once-day-by-day controlled discharge framework with a quick beginning of activity and diminished gastric irritancy. The goal was accomplished in Naprelan®; it has a demonstrated beginning of relief from discomfort inside 30 min that endures up to 24 h and is well-tolerated. The numerous benefits of the IPDAS® innovation incorporate high-thickness multiparticulate definition, GI security for all the more locally aggravation drugs (e.g., NSAIDs), benefits of multiparticulate in a tablet structure, and quick beginning whenever required [(15)] .

GeoClock®

Skye Pharma built up another oral drug delivery innovation, GeoClock®, as chronotherapy-centered press-covered tablets. GeoClock® tablets have a functioning medication inside an external tablet layer comprising a combination of hydrophobic wax and weak material to get a pH-free slack time before center medication conveyance at a foreordained delivery rate. This dry covering approach is intended to permit the coordinated arrival of both lethargic delivery and prompt delivery dynamic centers by delivering the inward tablet first, at which point, the encompassing external shell step by step breaks down.

Notwithstanding controlled delivery, the GeoClock® innovation likewise has applications for the improved arrival of colonic medication conveyance just as for numerous heartbeat drug conveyance to convey dosages of medication at explicit occasions for the day. Utilizing SkyePharma's exclusive GeoClock™ innovation, Lodotra™ appeared as an uncommonly formed tablet, which, once ingested, did not deliver the dynamic fixing, prednisone, until

around 4 h after the fact. Lodotra™ has been planned so the greatest plasma levels arrive 6 h after consumption. This empowers a patient to swallow the tablet at 10 p.m. before resting, with the portion of prednisone not being delivered until 2 a.m. what's more, arriving at greatest plasma levels at 4 a.m., which is viewed as the ideal planning to soothe the solidness and torment on strolling. This evening time discharge detailing is particularly fit to the treatment of early morning firmness, which is related to rheumatoid joint pain brought about by the checked arrival of fiery cytokines, including interleukin-6 in the early hours of the morning [(15)].

Uniphyl®

Uniphyl (theophylline, anhydrous) tablets in a controlled-release system allow a 24-h dosing interval for the patients. Uniphyl administered in the fed state is completely absorbed after oral administration [(16)].

PULSYS™

Middle Brook Pharmaceuticals, Inc. has built up a delivery innovation called PULSES, which empowers pulsatile conveyance or conveyance in quick explosions of specific medications. The innovation gives the drawn-out delivery and retention of a medication. The organization's PULSES item MOXATAG (amoxicillin broadened discharge) tablets, 775 mg are utilized for the treatment of pharyngitis/tonsillitis optional to Streptococcus pyogenes, ordinarily known as strep throat, for grown-ups and pediatric patient's age 12 and more seasoned. MOXATAG's once-day-by-day expanded delivery tablet comprises three segments: One quick delivery and two postponed discharge segments. The three segments are consolidated in a particular proportion utilizing its PULSES innovation to draw out the arrival of amoxicillin from MOXATAG contrasted and quick delivery amoxicillin[(15)].

Cover-HS

Cover-HS is the first once-day-by-day plan of an antihypertensive/ against anginal specialist that utilizes a high-level tablet covering and a novel drug delivery system to impersonate the body's regular 24 h circadian varieties in pulse and pulse. This novel conveyance innovation, called COER-24™ (Controlled-Onset-Extended-Release), was created related to Alza Corp. Cover-HS is the lone controlled-discharge verapamil detailing that is at present affirmed with a sign for the administration of both (hypertension) and angina pectoris (chest torment).

Accessible in both 180 mg and 240 mg tablets, Covera-HS is intended for oral dosing at sleep time. The pinnacle centralization of Covera-HS is conveyed in the early waking hours when circulatory strain and pulse are increases at their most noteworthy rate. There is insignificant medication conveyance during rest when pulse and pulse are at their physiologic most minimal [15].

Time multiple action delivery systems (TMDS)

This system controls discharge rates for numerous fixings inside a solitary tablet in a customized way. TMDS innovation considers the arrival of more than one dynamic fixing in a solitary tablet definition to be delivered in various profiles over a long period [16].

Geomatrix™

Another delivery gadget, as a multi-facet tablet, has as of late been proposed for steady medication discharge dependent on Geomatrix® Technology. It comprises a hydrophilic grid center, containing the dynamic fixing and a couple of impermeable or semi-penetrable polymeric coatings (films or compacted boundaries) applied on one of the two bases of the center. The Geomatrix™ innovation is applied to accomplish tweaked levels of controlled arrival of explicit medications and can accomplish concurrent arrival of two unique medications and various rates from a solitary tablet. The presence of the coatings alters the hydration/expanding pace of the center and decreases the surface region accessible for drug discharge (16). These halfway coatings give a balance of the medication disintegration profile; that is, they decrease the delivery rate from the gadget and shift the run-of-the-mill time-subordinate delivery rate toward consistent medication discharge. To accomplish controlled delivery, a complex tablet was developed utilizing two essential segments, hydrophilic polymers, for example, HPMC, and surface-controlling obstructions. The dynamic stacked center surface that is accessible for drug discharge when presented to the liquid is constrained by obstruction layers. Utilizing this novel innovation, SkyePharma has created Lodotra™, containing a rheumatoid joint pain drug. Lodotra™ conveys the dynamic drug fixing at the most appropriate season of day to treat the illness. Benefits of the Geomatrix™ innovation are their capacity to be effortlessly consolidated into the creation line, to be produced by promptly accessible gear, reproducibility, adequacy, the flexibility of delivery control systems, controlled arrival of ineffectively solvent medications, coordinated arrival of medications, bi-

phasic arrival of medications, the arrival of at least two medications at various rates, the beat arrival of medications, and well-being of utilization [15].

OSDRC technology

The regular dry-covered tablet (DC) strategy requires center tablet arrangement previously, and hence, the muddled methodology of the ordinary DC technique expands the assembling cost and the possibility of disappointment, which may prompt an ascent in center tablet supply. To tackle this issue OSDRC-innovation (one-venture dry covered tablet framework, and OSDRC-system) was built up that utilizes a two-fold design punch (focus punch and external punch) taking into account dry-covered tablets to be collected in a solitary run (15). The assembling interaction comprises three stages: Base layer (the first external layer) pressure, center pressure, and entire tablet pressure, which incorporates the upper layer and side layer (the second external layer). Since the tablets are created in a solitary advance while the punches make one revolution on a turntable, there could be not, at this point any requirement for a different stage to convey the center [16].

Diffutab®

Diffused innovation empowers altered delivery profiles and district explicit conveyance. The Diffutab innovation fuses a mix of waxes and hydrophilic polymers that control drug discharge through dissemination and disintegration of a grid tablet. Diffutabs are especially valuable for high-portion items and medications that require supported delivery as well as once-a-day dosing. Eurand applied this innovation to both dissolvable and insoluble items. The benefits of Diffutabs are high medication stacking, supporting supported delivery, and once-a-day dosing, as lattice tablets use a blend of water-solvent particles and dynamic medications [15].

Orbexa®

Orbexa innovation is a multiparticulate framework that empowers high medication stacking and is reasonable for items that require granulation. Eurand's Orbexa innovation produces dots of controlled size and thickness utilizing granulation spheronization and expulsion strategies. These dots give higher medication fixation than different frameworks, can be covered with practical polymer layers for extra delivery rate control, are adaptable, and are appropriate for use with touchy materials, such as compounds. Eurand's Orbexa innovation

can be utilized for gastric insurance, postponed discharge, supported delivery, site-explicit delivery, pulsatile delivery, complex delivery design, the partition of inconsistent, and blend items. Orbexa dots can be filled into cases or single-portion sachets [15].

Minitabs®

Eurand's Minicabs are small (2 mm×2mm) tube-shaped tablets covered with a useful film to control the pace of medication discharge. Eurand Minitabs contain gel-shaping excipients that control the medication discharge rate. Extra layers might be added to additional control the delivery rate. The tablets are filled into cases, permitting a mix of numerous medications or potentially different delivery profiles in a similar measurement structure. The Eurand Minitabs can be planned as lattice tablets before additional covering. Eurand Minicabs can likewise be utilized as a sprinkle on food. Eurand Minitabs joins the effortlessness of tablet detailing with the refinement of multiparticulate frameworks, appropriate for high medication stacking, and can be utilized as a sprinkle for pediatric and geriatric patients who experience issues gulping tablets [16].

CURRENT AND FUTURE DEVELOPMENT

The future of chronotherapeutics and more specifically the future of delivering drugs in a pulsatile manner seem to be quite promising as in certain diseases states pulsatile release exhibit several advantages over the traditional zero or first order drug delivery mechanism.

Pulsatile drug delivery system can either be time controlled or site specific single or multiple units. At a moment pulsatile release (site or time specific) most often is achieved by using different polymers in coating layers or by changing the coating thickness [17].

CONCLUSION

Currently, oral drug delivery is still the preferred route due to the high patient fulfillment, ease in administration, and elasticity of its formulations. There is a steady need for new delivery systems to provide increased therapeutic profit to the patients. While sustained and controlled-release products provide a desired therapeutic impact, drop brief of diseases following organic rhythms, circadian issues, peptic ulcer, high blood pressure, osteoarthritis, and asthma which want chrono pharmacotherapy. Circadian rhythm of the body is a widespread concept for knowledge of the most reliable want of drug within the body. Pulsatile drug delivery is one such system that, through handing over drugs in the proper region, time, and amounts, holds

proper assures of gain to the patients suffering from chronic problems. A sort of structures like stimuli, time, externally regulated multiparticulate regulated pulsatile thus conniving of right pulsatile drug transport will enhance the patient achievement, foremost drug delivery to the goal site and minimizes the undesired outcomes. We are sure that with an increase in technological development and higher design parameters, those obstacles can be overcome inside the close to destiny and wider variety of patients will be significantly benefited from this system.

REFERENCES

1. V.N. Sirisha et al., Pulsatile Drug Delivery System- A Review, international Journal of pharmaceutical Research & Allied Sciences, Vol 1, Issue 3, 2012, 13-23.
2. Aerpulla M. et al., Pulsatile Drug Delivery System, International Journal of Creative Research Thoughts, Vol 10, Issue 11, 2022, 366-373.
3. Sinchu Y.et al., pulsatile Drug Delivery System -A Review world Journal of pharmaceutical And Medical Research, Vol 4, Issue 12,2018, 130-142.
4. Firdos H. et al. , A Review on Pulsatile Drug Delivery System, International Journal of pharmacy Research & Technology, Vol 12, Issue 2, Jan- 2022, 10-23.
5. Dash S. et al., pulsatile Drug Delivery System (PDDS): A cronotherapeutic Approach for Optimum Therapy, Journal of Pharmaceutical Research International, vol34, Issue 31B, 2022, 28-45.
6. Devireddy S. K. et al., A literature review on Pulsatile Drug Delivery System, International Journal of pharmaceutical sciences Review and Research, Vol 72, Issue 2, January - February 2022, 7-16.
7. Mali A. D. et al., An updated review on Pulsatile Drug Delivery System, International Journal of Advances in Pharmaceutics, Vol 4, Issue 4, 2015, 16-22.
8. Yadav R. et al., Pulsatile Drug Delivery System- A Systematic Review, International Journal of pharmaceutical sciences and Research, Vol 14, Issue 1, 2023, 129-141.
9. Rajput M. et al., Pulsatile Drug Delivery System : A Review, international Journal of Research in Pharmaceutical and Biomedical sciences, Vol 3, Issue 1, Jan- Mar 2012, 118-124.
10. Sharma A. R. et al., Pulsatile Drug Delivery System: An overview, Asian Pacific Journal of health Sciences, Vol 5, Issue 3, 2018, 260-270.

11. Singh D. K. et al., Pulsatile Drug Delivery System: An overview, International Journal of current pharmaceutical review and Research, Vol 2, Issue 2,May-July 2011, 55-80.
12. P.SS. prasanna Kumar et al., A Review on Pulsatile Drug Delivery System, International Journal of pharmaceutical sciences and Research, Vol 14, Issue 7, 2023, 3246-3254.
13. Singh N. P. et al., Pulsatile Drug Delivery System: A Review, world Journal of pharmacy and pharmaceutical Sciences, Vol 5, Issue 5, 2016, 479-491.
14. Singh A. et al., Pulsatile Drug Delivery System: an Approach of Medication according to Circadian Rhythm, Journal of Applied Pharmaceutical Science, Vol 2, Issue 3, 2012, 166- 172.
15. Jain. D. et al., Recent Technologies in Pulsatile Drug Delivery System, Biomatter, Vol 1, Issue 1, 2011, 1-9.
16. Venkataswamy R. et al., Review Article on Pulsatile Drug Delivery System, Asian Journal of pharmaceutical And Clinical Research, Vol 14, Issue 6, 2021, 49-59.
17. Grover C. et al., A Comprehensive Review of Pulsatile Drug Delivery System, The Pharma Innovation, Vol 1, Issue 7, 2012, 99-104.