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PULSATILE DRUG DELIVERY SYSTEMS AND THEIR METHODOLOGIES

Shaik Farooq Ahmed, Bandaru Hemanth kumar, Prasanthi D.
G.Pulla Reddy College of Pharmacy, Hyderabad, Telangana, India
Corresponding Author:
Dr.D.Prasanthi, Associate Professor, Department of pharmaceutics, G.Pulla Reddy College of Pharmacy, Hyderabad, Telangana,India. MAIL I.D: prasanthidhanu@gmail.com

ABSTARCT

This review determines introduction to Pulsatile drug delivery system, necessity of PDDS, conditions that demand PDDS, advantages and disadvantages of PDDS, release pattern, disease that require the PDDS, mechanism of drug release in PDDS, methodologies to develop the PDD, marketed products and evaluation. PDDS have been attracted more because they are having multiple benefits over conventional dosage forms and they will deliver the drug at the right time and in the right amount and thus they are providing spatial and temporal delivery and increasing the patient compliance. The mechanism of drug release is rapid after welldefined the lag time. A pulse has to be designed in such a way that a complete and rapid drug release is achieved after the lag time which should match body's circadian rhythms with the release of drug which increases the efficacy and safety of drugs by proportioning their peak plasma concentrations during the 24 hours in synchrony with biological rhythm.These systems are beneficial for the drugs having chronopharmacological behaviour such as drug used in treatment of rheumatoid arthritis, osteo arthritis and ankylosing spondylitis like inflammatory disorders. Diseases wherein PDDS are to be used includes peptic ulcer, asthma, cardiovascular diseases, arthritis, and attention deficit syndrome in children, cancer, diabetes, and hypercholesterolemia. Therefore Pulsatile drug delivery is one such systems that becametrendy by delivering drug at the right time, right place and in right amounts, holds good promises of benefit to the patients suffering from chronic diseases.

KEY WORDS

Pulsatile drug delivery system, biological rhythm, lag time, chrono-pharmacological behaviour, inflammatory disorders.

Introduction

Pulsatile drug delivery system (PDDS)

Pulsatile drug delivery is defined as release of certain amount of molecules in a rapid and transient manner within a short period immediately after a predetermined off-released period. These systems have a mechanism of delivering the drug where the drug can be released rapidly and completely after a lag time, i.e., a period of no drug release. This release pattern is known as pulsatile release.

PDDS are time-controlled drug delivery system. These systems are designed in a way to achieve time specific and site-specific delivery of drugs. In pulsatile drug delivery system the release pattern is according to the circadian rhythm of the body. Pulsatile release pattern is the most popular form of controlled drug delivery system because conventional systems with a continuous release are not ideal. Pulsatile systems are beneficial for the drugs those having Chrono pharmacological behaviour (1). Pulsatile drug delivery systems 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. (2).

Necessity of Pulsatile Drug Delivery Systems

There are many diseases and conditions where sustained release formulations do not show good efficacy. In such cases, Pulsatile DDS is applicable. Many functions in our body follow circadian rhythm, i.e., their activity increases or decreases with time. A number of hormones like renin, aldosterone, and cortisol show daily as well as timely fluctuations in their blood. Pulsatile drug delivery system release pattern depends up on the Severity of diseases and time dependent like bronchial asthma, myocardial infarction, angina pectoris, rheumatic disease, ulcer, and hypertension. Sharp increase in asthmatic attacks have been reported during early morning hours. In such condition supplement of drug at particular time rather than maintaining constant plasma drug level is beneficial. Administration of drug at bedtime, which releases drug as a burst after the time of administration (during morning

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hours), would be ideal in this case. It prevents heart attacks in the middle of the night and the morning stiffness typical of people suffering from arthritis (3).

There are many conditions that demand pulsatile release like:

Secretion of hormones, acid secretion in stomach, gastric emptying, and gastrointestinal blood transfusion all these follows circadian rhythm. Bronchial asthma, myocardial infarction, angina pectoris, rheumatic disease, ulcer, and hypertension all the above diseases follows circadian rhythm and hence chronopharmacotheraphy possible. The lag time is required for the drugs that undergo degradation in gastric acidic medium (e.g.: peptide drugs) and irritate the gastric mucosa or induce nausea and vomiting.Targeting a drug to distal organs of gastro-intestinal tract (GIT) like the colon requires that the drug release is prevented in the upper two-third portion of the GIT.

Advantages of pulsatile drug delivery system:

1. Increases absorption and bioavailability of the drug when compared to conventional, immediate release or sustained release drug due to its ability to release drug in a burst manner, at target site of absorption.

2.Site targeting allows delivery of drugs which are poorly bioavailable that would get destroyed in higher GI tract environment e.g. (peptide and protein molecules)

Reduces side effects. Reduces drug interaction due to lower cytochrome P450 isoenzymes. Improved patient compliance.

3.Extended daytime or nighttime activity.

4.Patients in the therapy require daily fewer dosage units and hence daily cost is lowered.

5.Drug targeting to specific site like colon.

6.Pulsatile drug delivery system allows site-specific release for local treatment of diseases. Drug release is unaffected by change in pH of the GI tract, viscosity of lumen contents, and agitation rate of GI tract.

7.The system can be utilized for many solid dosage forms like granules, microspheres, micro particles, tablets, capsules, and pellets (4).

Disadvantages of pulsatile drug delivery system:

1.Lack of manufacturing reproducibility and efficacy.

2.Low capacity of drug loading and incomplete release of drug.

3.Large number of process variables.

4. It involves multiple formulation steps.

5.Cost of production is high.

6.Need of advanced technology.

7.Trained/skilled personal needed for manufacturing (5]

Release pattern in pulsatile drug delivery:

Pulsatile drug delivery is capable of releasing the drug after the lag time or predetermined time delay known as pulsatile drug delivery system. In pulsatile drug delivery are mostly designed for constant drug release over a prolong period of time. pulsatile delivery systems are characterized by a programmed release of drug, as constant drug blood level may not always be desirable (6). Drug release profiles from pulsatile systems is explained in Figure 1.

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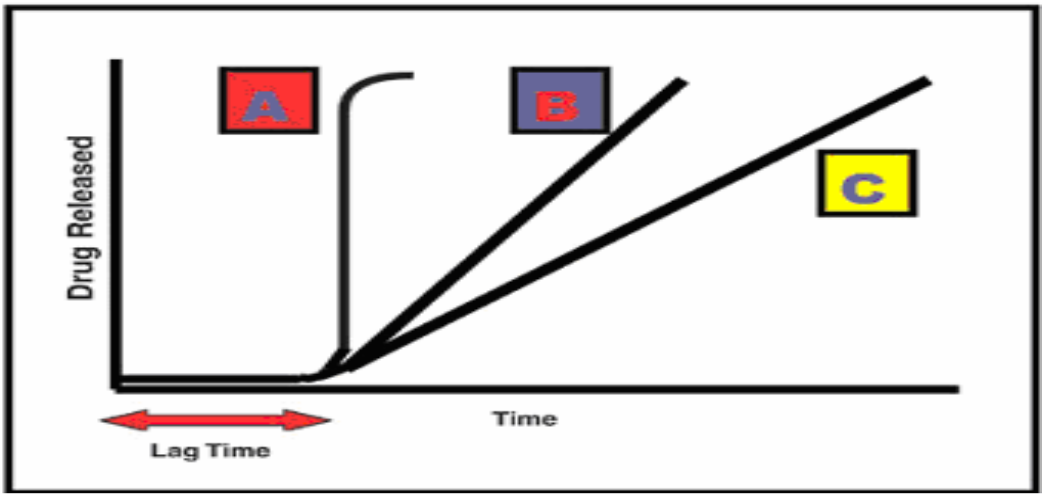

Figure 1 Drug release profiles of PDDS.

a = drug release as a "pulse" after a lag time

b = rapid and complete delivery of drug after a "lag time"

c = constant drug release over a prolonged period after a "lag time.

Table 1. Diseases that require "Pulsatile drug delivery": (1)

Disease	**Chronological behaviour**	**Drugs used**
Peptic ulcer	Acid secretion is high during afternoon and at night.	H2 blockers.
Cancer	The blood flow to tumours is threefold greater during each daily activity phase of the circadian cycle than during the daily rest phase.	Vinca Alkaloids, Texans.
Duodenal ulcer	Gastric acid secretion is maximum during night, while gastric and small bowel motility and gastric emptying are all slower at night.	Proton pump inhibitors
Neurological disorders	Epilepsy and the behavioral classification of convulsive events.	MAO-B inhibitor
Hypercholesterolemia	Cholesterol synthesis is generally higher during night.	HMG CoA reductase, Inhibitors
Diabetes mellitus	Increase in the blood sugar level after meal.	Sulfonylurea, Insulin
Arthritis	Level of pain increases at night.	NSAIDs, Glucocorticoids.

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Cardiovascular diseases	BP lowest during the sleep and rises steeply in the early morning.	Nitro-glycerine, calcium channel, blocker, ACE inhibitors
Asthma	Asthma exacerbation during night or at early morning.	B2 agonists, Antihistamines
Attention deficit syndrome	Increase in DOPA level in afternoon.	Methylphenidate

Mechanism of drug release from pulsatile drug delivery system:

The drug release from Pulsatile drug delivery system occurs in following ways:

Diffusion:

Water diffuses into the interior of the particle and when the particle meets aqueous fluids in the gastrointestinal tract, the resultant drug solutions diffuses across the release coat to the exterior.

Erosion:

The particles are released gradually by the erosion of the coatings on the particle system Some coatings are designed to erode gradually with time, this results in the release of drug contained within the particle/system.

Osmosis:

An osmotic pressure can be built up within the interior of the particle when suitable osmotically active agent is used. Due to the developed osmotic pressure, the drug is forced out of the particle into the exterior through the coating (2).

Methodologies to develop Pulsatile drug delivery systems:

Pulsatile drug delivery system can be broadly classified into three classes as shown in

figure no 2

I. Time controlled pulsatile drug delivery

II. Stimuli induced pulsatile drug delivery

III. Externally regulated pulsatile drug delivery.

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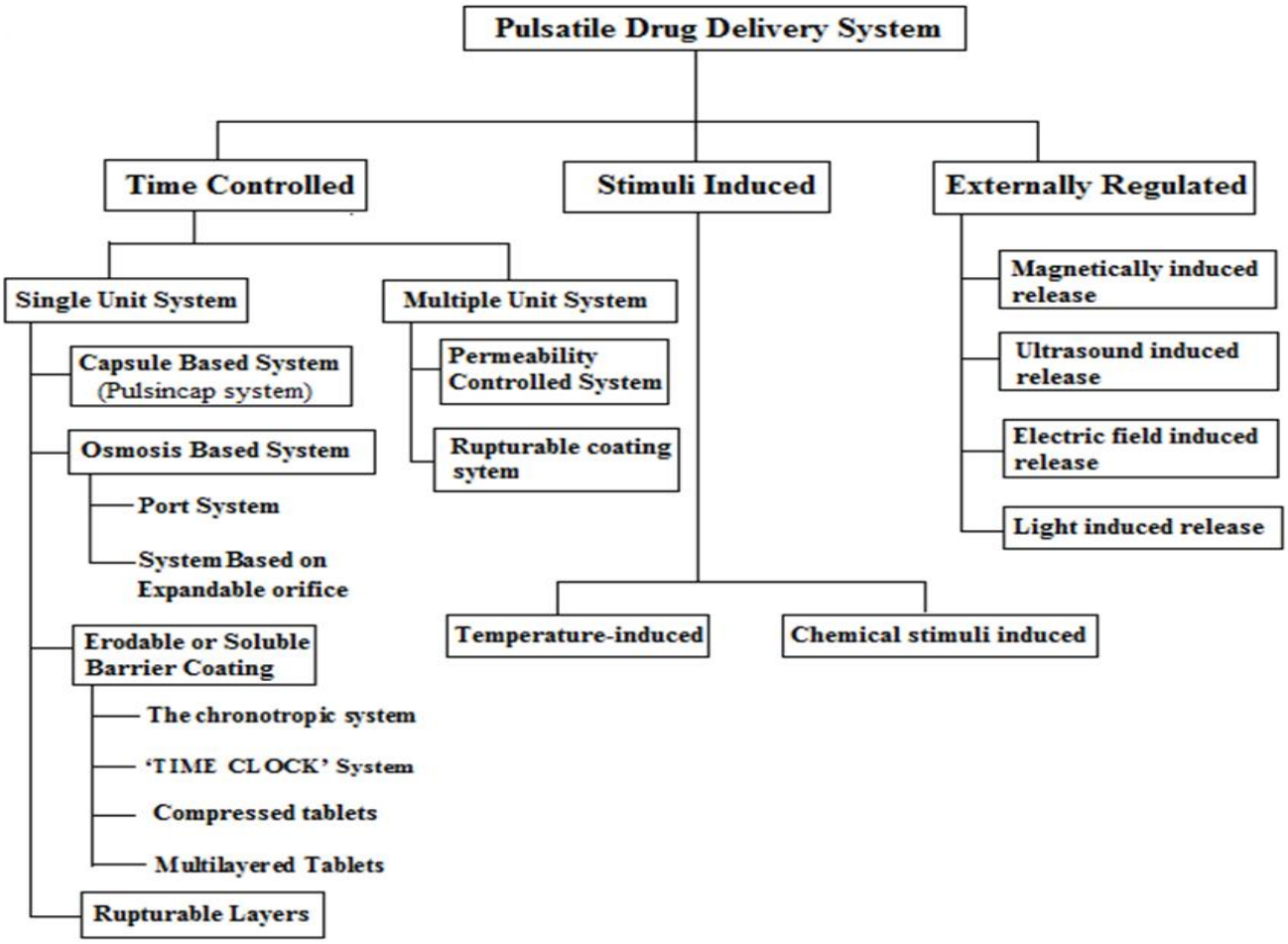

Table 2 : Classification of Pulsatile drug delivery system (7).

I. Time controlled pulsatile release system:

In time controlled drug delivery system, when can see the release pattern after a specific time interval in order to mimic the circadian rhythm. Time controlled drug delivery system can be classified based on rupturing of membrane or erosion of membrane. Time dependent dosage forms are designed and formulated in such a way that they should release their drug load after a predetermined lag time. Time controlled pulsatile drug delivery systems are further classified into single- and multiple-unit systems. Single-unit systems are mostly formulated either as capsule-based or osmosis-based systems. The pulsatile release is induced by changing membrane permeability or by coating with a eroding/soluble or rupturable coating (7).

Single unit system

Capsule based systems:Single-unit systems are mostly developed in capsule form. The pre determined time is controlled by using a plug, which gets pushed away by mechanism of swelling or erosion, and the drug is released as a pattern of "Pulse" from the insoluble capsule body. When this capsule meets the dissolution fluid, it swells; and after a predetermined time, the plug pushes itself outside the capsule and the drug is released rapidly. Polymers used for designing of the hydro gel plug were various viscosity grades and they are as follows:

1. Insoluble, permeable & swellable polymers (e.g., polymethacrylates)

2. Erodible compressed polymers like hydroxypropylmethyl cellulose, polyvinyl alcohol, Polyethylene oxide)

3. Congealed melted polymers like saturated polyglycolated glycerides, glyceryl monolete.

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

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5. Alternative to Pulsincap plug is erodible of hydroxyl propyl methylcellulose (HPMC K100M, HPMC K15M, and HPMC K4M), poly methyl follows methacrylate's, poly vinyl acetate and poly ethylene oxide (8).

The length and diameter of the plug and the point at which it is inserted into the capsule controls the lag time. The mechanism of drug release from the capsule can be understood from the following figure no 2.

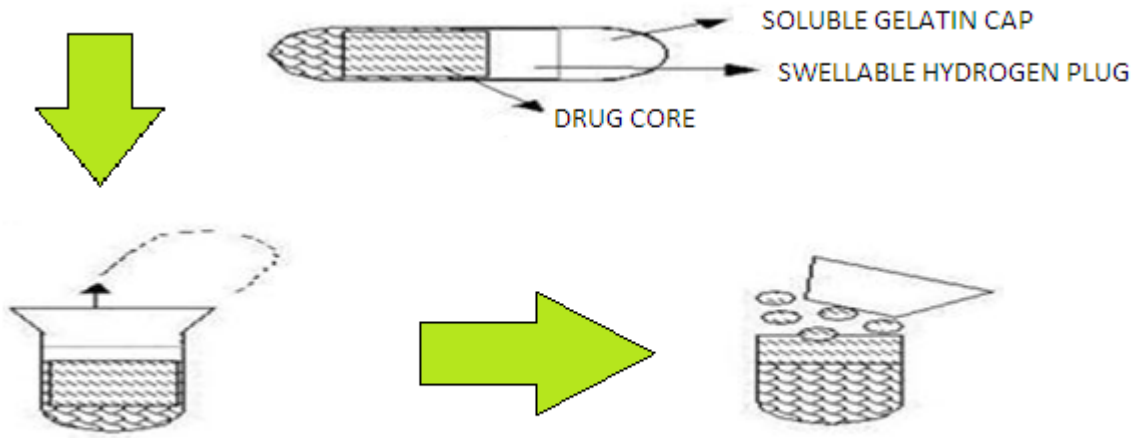

Figure 2: Design of Pulsincap system

A. Port systems:

Osmosis based systems are also called as **Port systems**. They mainly consists of a capsule coated body with a semipermeable membrane. Inside the capsule, there will be an insoluble plug consisting of osmotically active agent and the drug formulation. When this capsule meets the dissolution fluid, the semipermeable membrane allows the entry of water inside the capsule, which causes the pressure to develop, and the insoluble plug expels after a lag time (9).

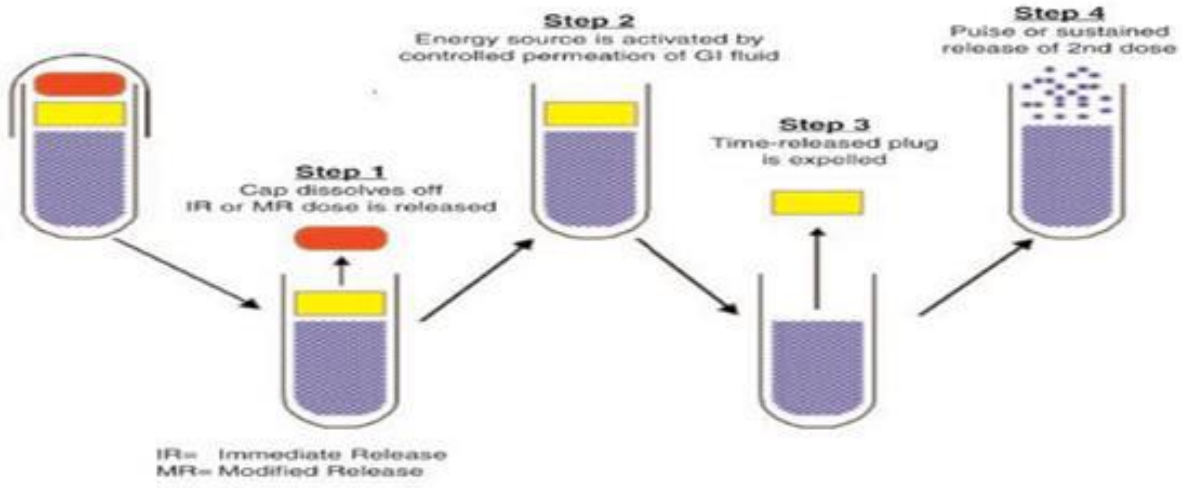

Figure 3 Drug release mechanism from PORT system.

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System based on expandable orifice:

The Expendable orifice system has a capsular system in which liquid drug is absorbed on highly porous particles. The release of drug molecules take place through a orifice of the semi permeable capsule body which is supported by an expanding osmotic layer, after that the barrier layer gets dissolved which causes the release of the drug. This system has advantage of extended release and also with high bioavailability. Delivering drug in the form of liquid is suitable for insoluble drugs, Polypeptides and Polysaccharides (). The capsular system delivers drug by the capsule's osmotic infusion of moisture from the body (figure no 5). The capsule wall is made up of an elastic material and possesses an orifice (10).

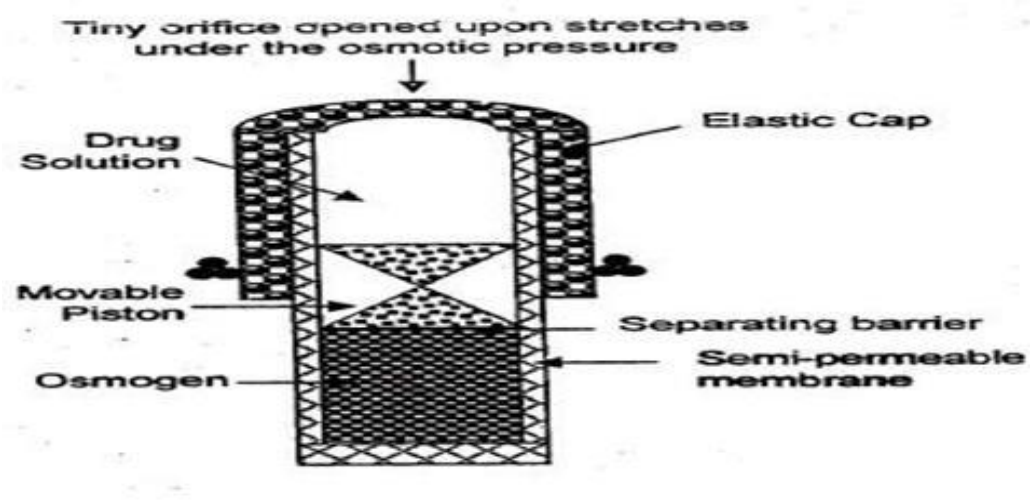

Figure 4: System based on expandable orifice

As the process of osmosis continues, the pressure inside the capsule increases and causes the stretching of wall. The orifice is small enough because of that when the elastic wall relaxes, the flow of drug through orifice essentially stops but when the elastic wall is distended beyond the threshold value, the orifice expands sufficiently to allow drug release at a required rate. Ex: elastomers, such as styrene-butadiene copolymer have been preferred. Pulsatile release was achieved after a lag time of 1-10 hrs, depending on the thickness of the barrier layer and that of permeability from semipermeable membrane. A capsule, which is designed for implantation, can deliver drug intermittently at intervals of 6 hours for 2 days**.**

Drug delivery systems with eroding or soluble barrier coating

Pulsatile drug delivery are mostly reservoir devices which are coated with a barrier layer.This barrier can get eroded or gets dissolved after a specific lag period, and the drug is subsequently released rapidly from reservoir core. The lag time is dependent on the thickness of the coating layer**.**

The chronotropic system

These systems are based upon a drug reservoir, which are surrounded with a soluble barrier layer that dissolves with time, and the drug releases at once after this lag time. Chronotropic® system consists of a core, which contains drug reservoir coated by a hydrophilic polymer HPMC. These are coated with enteric-coated filmto overcome intra-subject variability in the rate of gastric emptying. Thegrades of HPMC differ in thickness and viscosity controls the lag time and on set of action.

TIME CLOCK' System

The time clock system is a delivery device based upon solid dosage form which is coated by an aqueous dispersion. The core is coated by maintaining 75°C with aqueous dispersion of a hydrophobic surfactant layer (Beeswax,

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carnauba wax, poly {oxyethylene} - sorbiton monooleate) (Wilding et al., 1994). A water soluble coat is applied to improve adhesion to the core coat which can be seen in (figure no 6).The lag time could be controlled by varying the thickness of the film. After the particular lag time, i.e., the time required for rehydration, the core immediately releases the drug. Time clock system has shown reproducible results in vitro and in vivo (5).

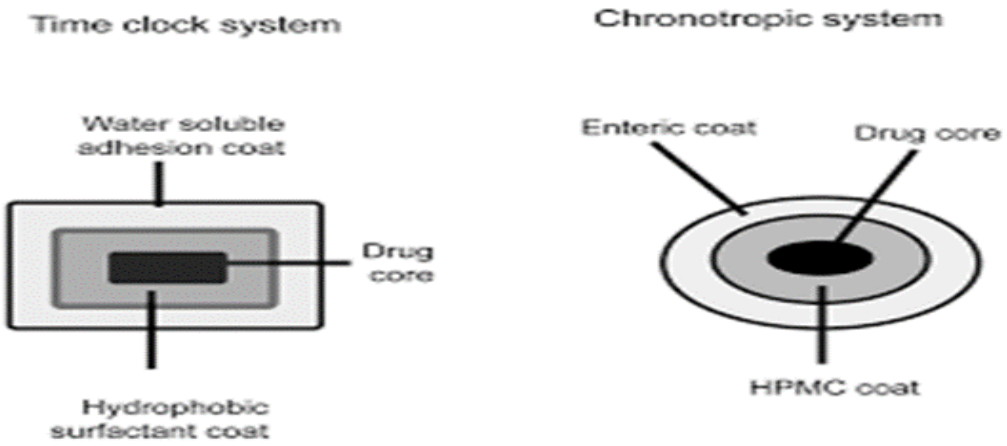

Figure 5: The 'TIME CLOCK' System and chronotropic system

Compressed tablets

Compression coating involves direct compression of both the core and the coat, this needs for use of coating solutions. The outer tablet of the compression-coated tablet consists of initial dose, which disintegrates rapidly in the stomach and the inner layer is formulated with components which are insoluble in gastric media but they are released in the intestinal environment. Cellulose derivative may be used for this purpose. Compression is easy on laboratory scale. The main disadvantages of this technique are:

High amounts of coating materials are needed and

it is difficult to position the cores correctly.

Following are the Advantages of Press-coated pulsatile drug delivery systems:

Protect hygroscopic,

light sensitive, acid labile drug,

they are simple and cheap in making (6)

D.**Multilayered Tablets**

Two pulses can be obtained from a three layered tablet incorporating two drugs containing layers separated by a drug-free gellable polymeric barrier layer. This three-layered tablet is coated on three sides with impermeable ethyl cellulose, and the top portion was not coated. When multi-layered tablet comes in contact with dissolution medium, the initial dose incorporated into the top layer gets released rapidly from the non coated surface. The second pulse is obtained when the bottom layer after HPMC layer gets eroded and gets dissolved. The time required for gelling or dissolution of the barrier layer controls the appearance of the second pulse. The gelling polymers are cellulose derivatives or polyvinyl alcohols of various molecular weights and the coating materials are ethyl cellulose, cellulose-acetate propionate, methacrylic polymers, acrylic and methacrylic co-polymers, and polyalcohols (12).

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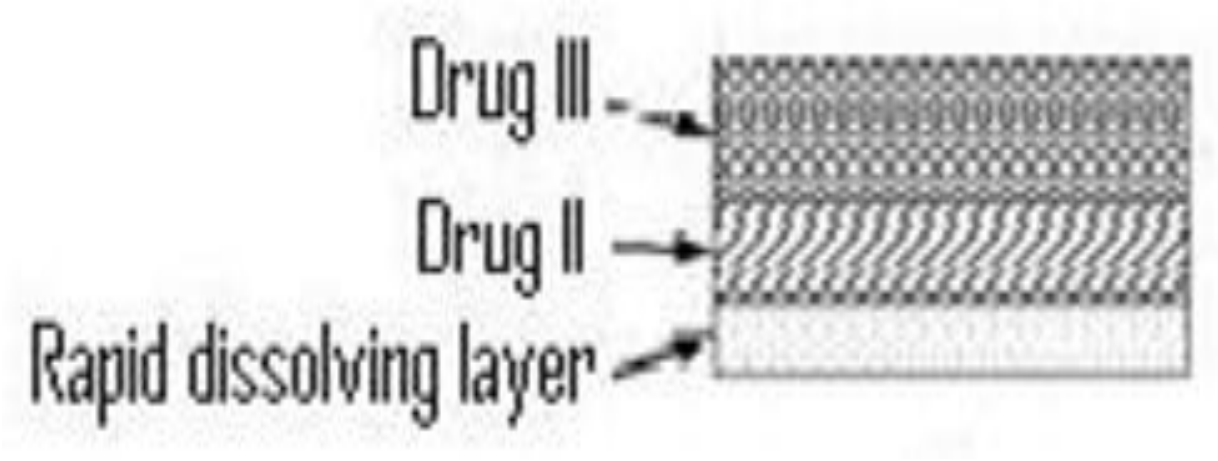

Figure 6 shows multi-layered tablets

Drug delivery system with rupturable layers or membranes:

These systems are based upon a reservoir system coated with a rupturable membrane. The outer membrane ruptures due to the development of the pressure by effervescent agents or swelling agents. A pulsatile system with rupturable coating on drug is present in hard gelatin capsules. These capsules were first coated with a swelling layer and then with an insoluble but water-permeable outer coating. These coated capsules when immersed in the release media could take up the media at a constant rate up to a point when the outer coating would rupture because of the pressure caused by the swelling layer (7).

Multiple-unit systems:

Multiple-unit drug delivery systems are mainly oral dosage forms consisting of a multiplicity of small discrete units, in which the active substance is present as number of small independent subunits. Multiple-unit systems are further classified as systems based upon change in membrane permeability and systems based upon rupturable coating.

The advantages compared to single-unit systems :

Gastric residence time is short

Reproducible gastric residence time

No risk of dose dumping

Flexible to blend pellets

Lowest transit time variability

Unique profiles

Capable of pulsatile release

Disadvantages:

Multiple manufacturing steps

Low drug load

Incomplete release

High cost of production (3).

Pulsatile system based on change in membrane permeability:

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Sigmoid type of release pattern was obtained from pellet core having drug and succinic acid coated with amino methylacrylate copolymers. The water in the medium dissolve succinic acid. The drug inside and acid solution increase the permeability of the polymer film. Actually permeability and water uptake of acrylic polymers with quaternary ammonium groups can be influenced by the presence of different counter-ions in the medium. It contains positively polarized quaternary ammonium group in the polymer side chain, which is always accompanied by negative hydrochloride counter-ions.

Eg. Sigmoidal release system (10).

Pulsatile systems with rupturable coating:

These systems is dependent on disintegration of the coat for the release of the drug. The pressure Required for the rupture of the coating is achieved by using different effervescent excipients, swelling agents, or by the osmotic pressure. The swelling agents used in this system include super disintegrants like sodium carboxymethyl cellulose, sodium starch glycollate, L-hydroxypropyl cellulose, etc. Upon absorption of water, the swellable layer expands, resulting in rupture of film with subsequent rapid drug release.

Eg. Time –controlled explosion system (TCES) (13)

2. Stimuli induced pulsatile release system.

In these systems the release of drug molecules stimulated by any biological factors like temperature or any other physical and chemical stimuli and these further classified in to the temperature induced system and chemical stimuli induced system. Temperature induced system temperature is the mostly widely used for triggering the signal for the variety of triggered or pulsatile drug delivery system for example thermo responsive hydrogel systems have been developed for the pulsatile release. in this system the polymers undergo swelling in response to the temperature which modulates the drug release in swollen state.

Chemical stimuli induced pulsatile release systems

1. PH sensitive drug delivery system A pulsatile drug release the drug when there is a change in the PH. It mainly consists of two components one is immediate release type and other one is pulsed release. based up on the required site of action and PH dependent polymer can be selected. By this drug release can be obtained at the site of action. Ph dependent polymers like cellulose acetate phthalate, polyacrylates and sodium carboxy methyl cellulose.

2. Glucose responsive insulin release device

In case of diabetes mellitus there is an some of the rhythm increase in the levels in the glucose in that case there is an requirement of injection of insulin at proper time. Several system have been developed to respond the changes in glucose concentration. When the glucose concentration increases in the blood glucose oxidase converts glucose in to the gluconic acid which causes a change in PH. This PH change induce swelling of the polymer which results in insulin release. example PH sensitive hydrogel containing glucose oxidase immobilized in hydrogel.

3. Inflammation induced pulsatile drug release.

during any injury, broken bone or any physical or chemical stress initiates the inflammation reactions. During this inflammation reactions hydroxy radicals are produced from these inflammation cells. So it is possible to treat patients with the inflammatory disease like rheumatoid arthritis using anti inflammatory drug incorporated HA gels a new implantable drug delivery system.(8).

Temperature-induced pulsatile release:

In these systems the polymer undergoes swelling or de-swelling phase in response of temperature i.e., Temperature triggers the release of therapeutic agents from several temperature responsive drug delivery systems for diseases accompanying fever.

Chemical stimuli-induced pulsatile release:

In these systems the polymer undergoes swelling or de-swelling phase in response to chemical reaction with membrane, alteration of pH and Inflammation induce.

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3.externally regulated pulsatile drug delivery system

Externally regulated pulsatile drug delivery includes:

1.Magnetically induced release

2.Ultrasound induced release

3.Electric field induced release

4.Light induced release

Magnetically induced release

Magnetic carriers receive their magnetic response to a magnetic field from the materials which are incorporated with magnetite, iron, nickel, cobalt etc. For biomedical applications, magnetic carriers must be water-based, biocompatible, non-toxic and non-immunogenic Ferrogel was fabricated by mixing poly (vinyl alcohol) hydrogels and Fe3O4 magnetic particles by freezing-thawing Cycles. Direct current magnetic field was applied externally to the ferrogel, the drug got accumulated around the ferrogel, but the accumulated drug spurt to the environment instantly when the magnetic fields instantly switched "off". Furthermore, rapid slow drug release could be tunable while the magnetic field was switched from "off" to "on" mode (14).

Ultrasound induced release

Ultrasound is mostly used to enhance the improvement of the drug permeation through biological barriers, such as skin. The interactions of ultrasound with biological tissues are divided into two broad categories: thermal and non-thermal effects. Thermal effects are associated with the absorption of the acoustic energy by the tissues or fluids. Non-thermal bio-effects are generally associated with oscillating or cavitating bubbles, but also include non-cavitation effects such as radiation pressure, radiation torque, and acoustic streaming (15).

Electric field induced release

Electrically responsive delivery systems are prepared by polyelectrolytes and are thus pH- responsive as well as electro-responsive. Upon the influence of electric field, electro responsive hydrogels generally changes its and bends, depending on the shape of the gel which lies parallel to the electrodes whereas deswelling occurs when the hydrogel lies perpendicular to the electrodes. An electro responsive drug delivery system was developed using poly (acrylamide-grafted-xanthan gum) hydrogel for transdermal delivery of ketoprofen (10).

Light induced release

Light-sensitive hydrogels have potential applications in developing optical switches, display units, and opthalmic drug delivery devices. The interaction in between the light and material can be used to modify drug delivery. When hydrogel absorb the light and convert it to heat, raising the temperature of composite hydrogel above its tolerable level, hydrogel collapses and result in an increased rate of release of soluble drug held within the matrix (16)

Table no 3 Marketed products of pulsatile drug delivery system (17)**:**

Brand name	Proprietary name	API	Mechanism and dosage form	Indication
CODAS®	Verelan® PM	Verapamil HCl	Extended release capsule Hypertension	Extended release capsule Hypertension
CONTIN®	Uniphyl®	Theophylline	Extended release tablet	Asthma
OROS®	Covera-HS®	Verapamil HCl	Extended release tablet	Hypertension

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DIFFUCAPS®	Innopran®XL	Propranolol HCl, Verapamil HCl	Extended release capsule	Hypertension
OROS®	Invega™	Paliperidone	Tablet	Schizophrenia
PULSYS™	Pulsincap™	Dofetilide	Rupturable system	Antiarrhythmic
OROS®	Concerta®	Methylphenidate HCl	Tablet	Anti-psychotic
PULSYS™	Moxatag™	Amoxicillin	Multiparticulate system	Infection
TIMERx®	OPANA®	Oxymorphone	Erodible/ soluble barrier coating ER Tablets	Pain management
CEFORM®	Cardiazem® LA Diltiazem HCl,	Verapamil HCl	Extended Release tablet	Hypertension
Physico-chemical modification of API	Pepcid®,	Famotidine	tablet	Ulcer
Physico-chemical modification of API	Zocor®	Simvastatin	Tablet	Hypercholesterolemia
PROCARDIA XL®	Procardia XL	Nifedipine	Sustained release	Hypertension

Evaluation of pulsatile drug delivery system:[10]

1. Preformulation study: Different physicochemical properties of drug and drug in excipient mass are evaluated in Preformulation study

2. *Drug excipients interaction study :*The Fourier transform infrared (FTIR) technique and Differential scanning calorimetry (DSC) can be usedto study the physical and chemical interactions between the drug and excipients used).

3. Evaluation of powder blend: Prepared powder blend are evaluated for Angle of Repose, Bulk Density, Tapped Density, Carr's index (or) %Compressibility, Hausner's Ratio.

4. Plug Thickness: Thickness of plug was measured using screw gauge. Plugs of different weights (50mg, 75mg, 100mg) are selected and thickness is measured using screw gauge. The test is carried out intriplicate.

5. Hardness: Hardness or Crushing strength (the force required to break a tablet in a diametric ccompression) of the plug is measured using Monsanto Hardness tester. It is expressed in Kg/cm^2().

6. Content Uniformity: Twenty capsules were randomly selected from each batch of the prepared formulations. The contents of the capsules were removed and powdered.From this sample 100 mg powder was accurately transferred in to 100ml volumetric flask and make up with methanol. The resultant solution was filtered through 0.45 µm filter paper and suitably diluted. Then the drug content was estimated spectrophotometrically by measuring the absorbance at respective wavelengths.

7. In vitro dissolution study: The in vitro dissolution study is performed usingdissolution test given in monograph or in standardliterature. In general case, dissolution media are 900ml of 0.1 M HCl for 2 hr (since average gastricemptying time is 2 hr) and 900 ml of phosphatebuffer pH 6.8 for 3 hr (average small intestinal transittime). After 5 hr, the dissolution medium is replacedwith pH 7.4 phosphate buffer (900 ml) and tested forthe drug release up to specific hour dissolution study.At the predetermined time intervals, specific volumeof dissolution media (1, 2,

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5, 10 ml etc..) are withdrawn, filtered through a 0.45 μm membranefilter, diluted, and assayed at wavelength maximausing a UV spectrophotometer (Vipul et al., 2012).

Table no 4 : Marketed Technologies of pulsatile drug delivery system(17)**:**

Here are few of the Marketed Technologies used in pulsatile drug delivery

Sl.no	Marketed Technologies
1.	OROS*
2.	Three dimentional printing*
3.	DIFFUCAPS*
4.	PulsincapTM
5.	Geomatrix technology

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