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A COMPREHENCIVE REVIEW ON FLOATING PULSATILE DRUG DELIVERY SYSTEM

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ABSTRACT

Conventional controlled release drug delivery systems are based on single-or multiple-unit reservoir or matrix systems, which are designed to provide constant or nearly constant drug levels over an extended period of time. Pulsatile drug delivery is one such system there by delivering drug at the right time, right place and in right amounts and holds good promises and provides benefit to the patients suffering from chronic problems like arthritis, asthma, hypertension etc. A single dosage forms provided an initial dose of drug followed by one release free interval after which second dose of drug is released, which is followed by additional release free interval and pulses of drug release. The ability to deliver a bioactive compound and therapeutic agent to a patient in pulsatile release profile is major goal in the drug delivery.

KEYWORDS: Chronotherapy, Floating pulsatile release tablet, Controlled release drug delivery.

INTRODUCTION

The main purpose of this study that, to develop an idea about floating pulsatile drug delivery system for obtaining no drug release during floating and in the proximal small intestine followed by pulsed drug release in distal small intestine. To achieve chronotherapeutic drug release of drug which used for treatment of rheumatoid arthritis, osteoarthritis, spondylitis, cardiovascular disease, and several hypertension syndrome which improve the patient compliance.[1]

Floating Pulsatile Drug Delivery System is the system form in which drug release in specific site and specific drug action at specific time. Floating drug delivery system have bulk density less than gastric fluid and so remain buoyant in stomach for prolonged period of time releasing the drug slowly at the desired rate from the system. Floating drug delivery systems (FDDS) are system in which to retain the drug in the stomach and are useful for drug that are poorly soluble or unstable in intestinal fluids. The underlying principle is very simple i.e., to make the dosage form less dense. The basic idea behind the development of such a system was to maintain a constant level of drug in the blood plasma inspite of the fact that the drug dose not undergoes disintegration. The drug usually keeps floating in the gastric fluid and slowly dissolves at a pre-determined rate to release the dosage form and maintain constant drug levels in the blood.[2]

The advantages of that system are that they can be retain in the stomach and assist in improving the oral sustained delivery of drugs that have an absorption window in particular region of the GIT. These systems continuously release the drug before it reaches the absorption window, thus ensuring optimal bioavailability. Different approaches are currently used to prolong the gastric retention time, like hydro dynamically balanced systems, swelling and expanding system, polymeric bioadhasive systems, modified shape systems, high density system and other delayed gastric emptying devices. The principle of buoyant preparation offers a simple and practical approach to achieve increased gastric residence time for the dosage form and sustained drug release.[3]

PULSATILE DRUG DELIVERY SYSTEM

Diseases where a constant drug levels are not preferred, but needs a pulse of therapeutic concentration in a periodic manner acts as a push for the development of “Pulsatile drug Delivery Systems”. In this system, there is rapid and transient release of a certain amount of drug molecules within a short time-period immediately after a predetermined off release

period. Various techniques are available for the pulsatile delivery like PH dependent systems, time dependent systems, micro-flora activated systems, etc. This can be designed as per the physiology of disease and properties of the drug molecule. In the body several physiological functions such as metabolism sleep pattern heart attacks are regulated by pulsed or transient release of bioactive substances at a specific time and site. Therefore to mimic the function of living system it is necessary to achieve pulsed release of certain amount of bioactive compounds at predetermined interval. Thus release pattern of such drug delivery is circadian pattern. The release of some drug is preferred in pulses. A single dosage forms provided an initial dose of drug followed by one release free interval after which second dose of drug is released, which is followed by additional release free interval and pulses of drug release. The ability to deliver a bioactive compound and therapeutic agent to a patient in pulsatile release profile is major goal in the drug delivery. This system is also called as time controlled system because the release is independent of the environment.[4, 5]

FLOATING DRUG DELIVERY SYSTEM

Floating drug delivery systems is one of approaches to achieve gastric retention to obtain sufficient drug bioavailability. This delivery systems is desirable for drugs with an absorption window in the stomach or in the upper small intestine. This have a bulk density less then gastric fluids and so remain buoyant in the stomach without affecting gastric emptying rate for a prolonged period and the drug is released slowly as a desired rate from the system. After release of drug, the residual system is emptied from the stomach. This result in an increased gastric retention time (GRT) and a better control of the fluctuation in plasma drug concentration. The major requirements for floating drug delivery system are.

• It should release contents slowly to serve as a reservoir.

• It must maintain specific gravity lower than Gastric contents (1.004 –1.01gm/cm3).

• It must form a cohesive gel barrier.[6]

1.1 CHRONOTHEREUPEUTICS

The term "chrono" is defined as every metabolic event undergoes rhythmic changes in time. Researchers have concluded that chronotherapeutics are refers to a treatment , method in which *in vivo* drug availability is timed to match rhythms of disease in order to optimize therapeutic outcomes and minimize side effects. It is based on the observation that there is an interdependent relationship between the peak-to-trough rhythmic activity in disease symptoms and risk factors, pharmacologic sensitivity, and pharmacokinetics of many drugs[8]

As more continues to be learned about chronobiology and chronotherapeutics, 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. The tradition of prescribing medication at evenly spaced time intervals throughout the day, in an attempt to maintain constant drug levels throughout a 24-hour period, may be changing as researchers' report that some medications may work better if their administration is coordinated with day-night patterns and biological rhythms.[1] living organisms are composites of rhythms with varying frequencies that may range from seconds to seasons.[7]

1.2 CHRONOBIOLOGY

Chronobiology is study of science concern with biological mechanism of diseases according to time structure. Chrono pertains time and biology means study, science or life.

1.3 CHRONOPHARMACOLOGY

Chronopharmacologycal study concern with study of variation of pharmacological action of various drug over a period of time of day.

1.4 CHRONOTHERAPY

Chronotherpy is coordination of biological rhythm and medical treatment is called as chronotherapy.

1.5 BIOLOGICAL RHYTHMS

A biological rhythm is a self-sustaining process inside the human body. It is defined as the, "process that occurs periodically in an organism in conjugation with and often in response to periodic changes in environmental condition". Our bodies' rhythm, also known as our biological clock, and the rhythm of the solar system that change night to day and lead one season into another. Our internal clocks are also dictated by our genetic makeup.[8]

There are 3 types of mechanical rhythms present in our body such as,

1. ULTRADIAN RHYTHMS

Ultradian rhythm:

Oscillation are shorter duration of action are known as ultradian rhythm. (More than one cycle per 24 hrs) e.g. 90 minute sleep cycle.

2. INFRADIAN RHYTHMS

Oscillations that are longer than 24 Hours are known as in radian Rhythms (Less Than One Cycle per 24hours).[7]

3. CIRCADIAN RHYTHMS

It is defined as Self-Sustaining, Endogenous Oscillations that occur with A Periodicity of about 24 Hours. Interestingly, the Term Circadian Is Derived from the Latin circa Which Means ―About and Dies Which Can Be defined as ―A Day. Normally, Circadian Rhythms Are Synchronized According To Internal Biologic Clocks Related To The Sleep-Wake Cycle.

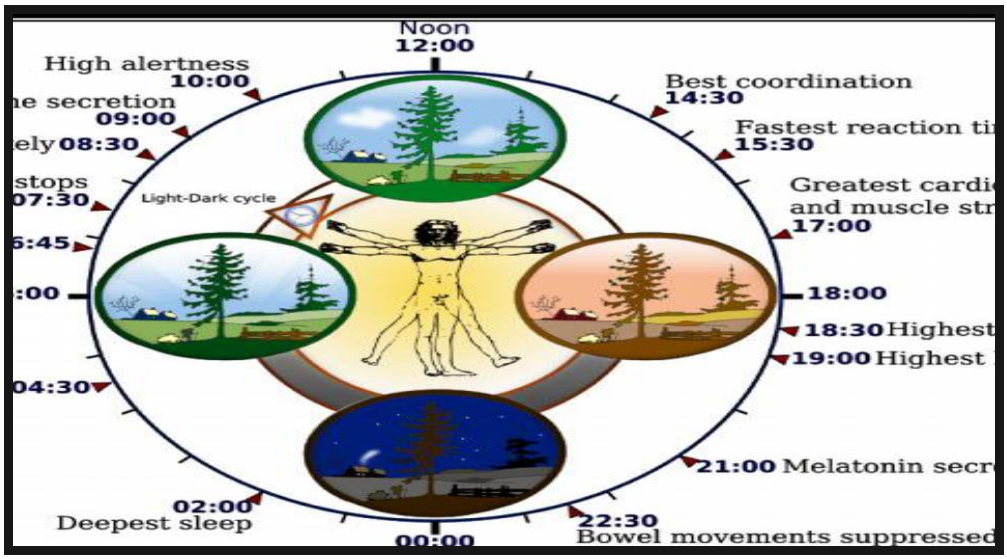

Fig. 1- Circadian rhythms.[8]

1.6. DRUG CANDIDATES SUITABLE FOR FPDDS

1. Drugs that have narrow absorption window in GIT.

E.G. L-Dopa, Paminobenzoic Acid, Furosemide, Riboflavin.

2. Drugs those are locally active in the stomach.

E.G. Misroprostol, Antacids.

3. Drugs those are unstable in the intestinal or colonic environment.

E.G. Captopril, Ranitidine HCL, Metronidazole.

4. Drugs that disturb normal colonic microbes.

E.G. Antibiotics used for the eradication of helicobacter pylori, such as Tetracycline, Clarithromycin, Amoxicillin.

5. Drugs that exhibit low solubility at high Ph values.

E.G. Diazepam, Chlordiazepoxide, Verapamil.[9]

1.7. ADVANTAGES

1. Drugs can be destroyed in higher gi tract environment. e.g, peptide and protein molecules.
2. It reduces dose of drug without decrease in therapeutic effects.
3. Ratio 0f decreases in side effects is high.
4. Decreases drug interaction due to lower cytochrome p450 isoenzymes.
5. Decreases effect 0f food.
6. Improved patient compliance.
7. It provides optimal treatment of diseases.
8. Programmed delayed release allows multiple dosing in a single dosage form.
9. Allows site specific release for local treatment of diseases.
10. Drug release is not affected by change in ph of the gastrointestinal tract,
11. Viscosity of lumen contents, and also agitation rate of gi tract
12. It is useful in drug having a short half-life.
13. Helpful in extended day time or night time activity
14. It avoiding the first pass metabolism e.g., protein and peptides.
15. Biological tolerance e.g., transdermal nitroglycerin.
16. It provides specific targeting site in intestine e.g., colon.
17. Used for time programmed administration of hormone and drugs.
18. Avoid gastric irritation of drug.
19. Improve drug instability in gastric fluid.
20. Lower daily cost to patient due to fewer dosage units are required in therapy.
21. Protection of mucosa from irritating drugs
22. Drug loss is prevented by extensive first pass.
23. Metabolism e.g. Proteins and peptide.
24. Avoid biological tolerance e.g., transdermal nitroglycerine.[10-12]

1.8. DISADVANTAGES

1. Floating system is not viable for those drugs that have solubility or stability problem in GIT.
2. These systems require a high level of fluid in the stomach for drug delivery to float over a stomach.
3. The drugs that are extensively absorbed throughout gastrointestinal tract, which undergo significant first pass metabolism, can only use for this system.
4. Lack of manufacturing reproducibility and efficacy is the major problem.

5. It requires large number of process variables.

6. Include batch manufacturing process.

7. Higher cost of production is involved.

8. Trained/skilled personal needed for manufacturing of dosage form.

9. It develops a 24 hours sleep wake syndrome, if after the treatment as the person sleeps for over 24 hours during the treatment. It's not quite common but the degree of risk is not identified.

10. Person may also be underprivileged of sleep sometimes.

11. Person become less productive during chronotherapy and staying awake till the other schedule might be bitun comfortable.

12. Person will have to take some time off from their busy normal schedule asits time taking therapy.

13. Medical supervision is obligatory for this therapy and regular consulting ofsleep specialists are recommended.

14. Person has to keep himself awake till the next sleep schedule so he have to get himself busy so that he stay awake till the other schedule.

15. Person undergoing therapy may feel unusually hot or cold sometimes.

16. Patient needs to consult the doctor regularly to avoid side effects.[13-15]

1.9 CLASSIFICATION OF PDDS

a) Time controlled system

1. Single unit pulsatile drug delivery system

a) Capsule based systems

b) Delivery system with rupturable coating

c) Osmotic system

d) Delivery System provided with erodible coating layer

2. Multiple unit pulsatile drug delivery system

a) System based upon rupturable coating

b) System based upon change in membrane permeability

1.9.1 TIME CONTROLLED SYSTEM

1. SINGLE UNIT PULSATILE SYSTEM

i. Capsule based system

A capsular system is an insoluble capsule body housing a drug and a plug. The plug is removed after a predetermined lag time owing to swelling, erosion, or dissolution. The lag time is continued by a plug that gets pushed away by swelling or erosion, releasing the drug as a pulse from the insoluble capsule body. The system is comprised of a water insoluble capsule enclosing the drug reservoir. A swellable hydrogel plug was used to seal the drug contents into the capsule body. When the capsule comes in contact with dissolution fluid, the plug gets swells, and after a lag time, the plug pushes itself outside the capsule and rapidly releases the drug. The length of the plug and its point of insertion into the capsule controlled the lag time. The body is closed at the open end with a swell able hydrogel plug. Upon contact with dissolution medium or Gastro-intestinal fluids, the plug swells, pushing itself out of the capsule after a lag time. This is followed by a rapid drug release. Manipulating the dimension and the position of the plug can control the lag time. For water-insoluble drugs, a rapid release can be ensured by inclusion of effervescent agents or disintegrants. This formulation does not cause GI irritation and it is overcome by enteric coating.

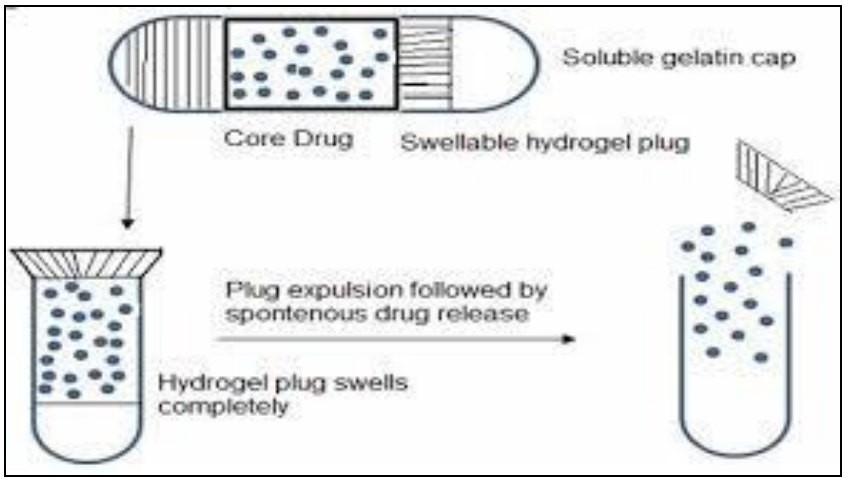

Fig. 2: Capsule based system.

ii. Delivery systems with rupturable coating layer

These systems consist of an outer release controlling water insoluble but porous coating subject to mechanically which induced burst phenomenon. Recently different systems based on hard gelatin capsules and tablet core were described, which all coated by inner swellable and outer rupturable layer. Including swelling, osmotic or effervescent additives in the

reservoir may attain the film rupture. By optimizing the system, drug release can be obtained at definite time period. Sungthongjeen et al developed a tablet system consist of core coated with two layers of swelling and rupturable coatings wherein they used spray dried lactose and microcrystalline cellulose in drug core and then core was coated with swelling polymer croscarmellose sodium and an outer rupturable layer of ethyl cellulose (fig.2). Further development of osmotic drug delivery using swellable core technology where in a formulation consists of a core tablet which consist of the drug and a water swellable component, and one or more delivery ports.[16]

iii. Osmotic systems

It consists of capsule which coated with a semi permeable membrane. A mysterious drug consisting of the osmotic ally active agents and drug formulations are integrated inside the capsule. When this capsule comes in contact with dissolution fluid, the semi permeable membrane allows the entry of water, which causes increase of pressure and the insoluble plug Expels after a lag time (fig.3).

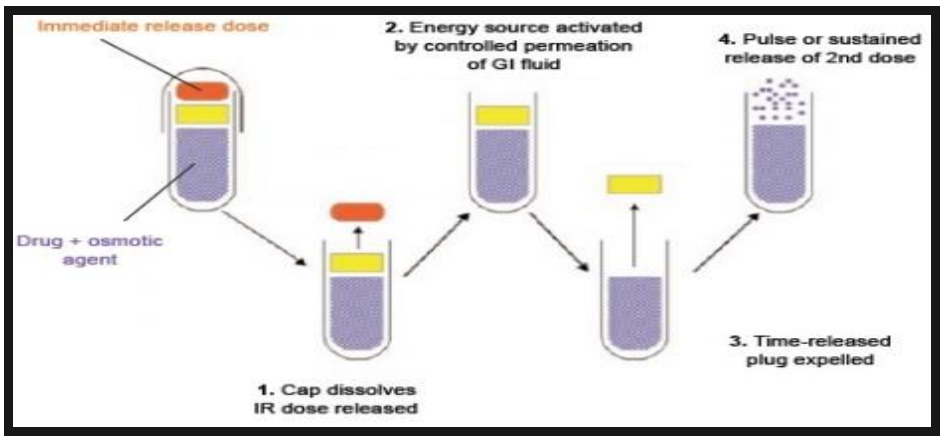

Fig. 3: Osmotic pulsatile drug delivery system.

iv. Delivery systems provided with erodible coating layers

In such systems the drug release is controlled by the dissolution or corrosion of the outer coat, which is applied on the core-containing drug (fig. 4, 5). The time dependent release of the active ingredient can be obtained by optimizing the thickness of the outer coat. An oral dosage form devised which use to release drugs subsequent in a deliberate time period after administration based on this concept. This system is composed of a drug-containing core and a hydrophilic swellable polymeric coating of HPMC, which is capable of delaying the drug release through slow interaction with aqueous fluids.

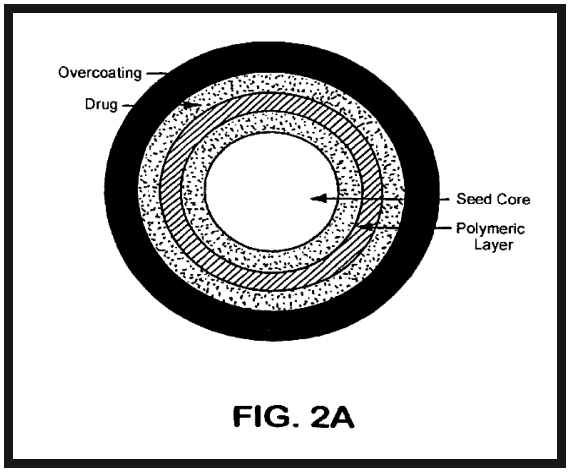

Fig. 4: Delivery systems with erodible coating layers.

2. MULTIPLE UNIT PULSATILE DRUG DELIVERY SYSTEM

A) Systems based upon change in membrane permeability

In this system drug is designed in such manner that, the drug releases is divided in doses over time intervals throughout a day use to produce a pulsatile curved deliberation with a time. In which the drug is formulated in a capsule form body containing three types of pellets. Each one pellet contains a core that comprises a drug and water-soluble modulating agent (e.g. Sodium chloride). The core is held in place with the heQH of binding agent like pvp. Each core is enclosed with water insoluble and water porous film forming and a hydrophilic agent. the thickness of the coating depends upon kind of pellet used to form drug formulation .when the capsule is exposed to the physiological environment it gets dissolved and pellets are exposed to the gastric environment .the rate of release is controlled by the virtual thickness on the pellets, the fraction of hydrophobic agent in coating and the proportion of osmotic agent in the pellet. The coating of ph in dependent material is given to ensure that it does not disturb predetermined release time intervals.[17]

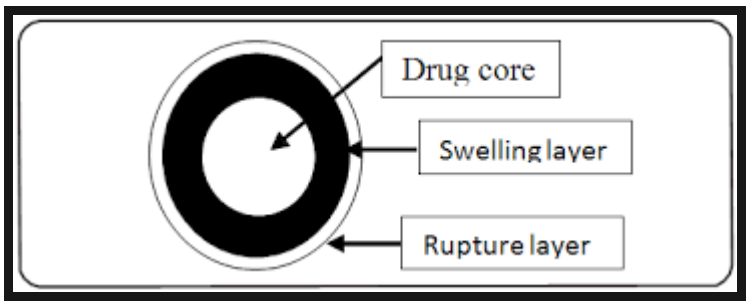

Fig. 5: Delivery Systems with Rupturable Coating Layer.

B) Pulsatile systems with rupturable coating

Pulsatile drug delivery system controls the rupture of membrane .the timing of release is controlled by the thickness of coating and amount of water soluble polymer used to achieve the pulsed release .the individual particle has the identical composition of internal core but the thickness of the external coating may be assorted. Multiparticulate system offers more advantages over single unit pulsatile system. these include no risk of dose dumping, flexibility of blending units with different release pattern and short gastric residence time. Many polymers and their type of devices are used to provide a pulsatile release of a drug. The devices are classified according to the type of polymer used which applied to increase the gastric residence of dosage forms and having lag phase followed by burst release. Such type of novel drug delivery has been attempted for,

I) Chronopharmacotherapy of diseases which show circadian rhythms in the pathophysiology.

II) For those drugs having absorption window in upper GIT.

III) For drugs having ph dependent solubility e.g. Verapamil HCL.

IV) Gastro retentive: better absorption from upper part of GIT for those drugs that are insoluble in lower GIT, thus avoid degradation.[18]

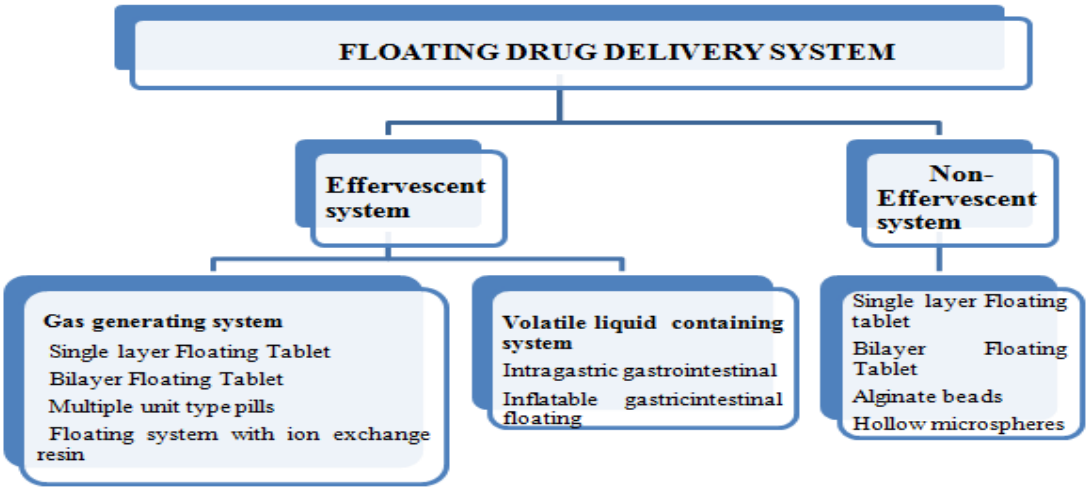

Fig. 6: Floating pulsatile drug delivery system.

1.10 Classification of Floating Drug Delivery.[19]

Floating drug delivery systems are classified depending on the use of two formulation variables:

1) **Effervescent systems**
2) **Non-effervescent systems.**

1) Effervescent Floating Dosage Forms

These are matrix types of systems prepared with the help of swellable polymers such as methylcellulose and chitosan and various effervescent compounds e.g. sodium bicarbonate, tartaric acid, and citric acid. They are formulated in such a way that when in contact with the acidic gastric contents, $C0_2$ is liberate and gas entrapped in swollen hydrocolloids which provides buoyancy to the dosage forms.

2) Non-effervescent Floating Dosage Forms

Non-effervescent floating dosage forms use a gel forming or swellable cellulose type hydrocolloids, polysaccharides, and matrix forming polymers like polycarbonate, polyacrylate, polymethacrylate, and polystyrene. The formulation method includes a simple approach of thoroughly mixing the drug and the gel-forming hydrocolloid. After oral administration this dosage form swells in contact with gastric fluids and attains a bulk density of < 1. The air entrapped within the swollen matrix imparts buoyancy to the dosage form. The so formed swollen gel-like structure acts as a reservoir and allows sustained release of drug through the gelatinous mass.

Table no 1: Diseases required pulsatile delivery is as follows.[20]

Diseases	Chronological Behavior	Drug Used
Peptic ulcer	Acid secretion is high in the afternoon and at night.	h2 blockers
Asthma	Precipitation of attacks during night or at early morning.	β2agonist,antihistamines
Cardiovascular diseases	BP is at its lowest during the sleep cycle and rises steeply during the early morning.	Nitroglycerin calcium channel blocker, ace inhibitors
Arthritis	Pain in the morning and more pain at night.	nsaid, glucocorticoids
Diabetes mellitus	Increase in the blood sugar level after meal.	sulfonylurea, insulin

1.12 DISEASES AND CHRONOTHERAPEUTICS

Diseases are presently targeted for chronopharmaceutical formulations which are have enough scientific backgrounds to justify PDDS as compared to the conventional drug administration approach .they include hypercholesterolemia, asthma, cancer, duodenal ulcer, arthritis, diabetes, neurological disorders, cardiovascular diseases (e.g. Hypertension and acute myocardial infarction) and colonic delivery. The rationale for chronotherapy/pulsatile release for each of these diseases will be briefly reviewed and given as follows.[21]

1) Cardiovascular Diseases

Cardiovascular diseases include hypertension and angina, or chest pain, also follow a definite circadian rhythm .in cardiovascular disease capillary resistance and vascular reactivity is higher in the morning and decreases latter in the day. Platelet agreeability is increased and fibrinolytic activity is decreased in the morning, which leading to a state of relative hyper coagulability of the blood. Because of this reason the frequencies of myocardial infarction and of sudden cardiac death are more during a period from morning to noon. Ambulatory blood pressure measurements show a significant circadian variation to characterize blood pressure .this variation is affected by a variety of external factors such as ethnicity, gender, autonomic nervous system tone, vasoactive hormones, and hematological and renal variables. Increased heart rate, blood pressure, imbalanced autonomic tone, circulating level of catecholamine controlling the cardiac arrhythmias show important circadian variation and trigger the genesis of the circadian pattern of cardiac arrhythmias. Atrial arrhythmias appear to exhibit circadian pattern usually with a higher frequency in the daytime and lower frequency in the night time with the abnormal foci under the same long term autonomic regulation as normal pacemaker tissue. According to study ventricular atrophy arrhythmias shows late morning peak in the patients with myocardial infarction sometime in the distant past morning peak and afternoon peak in patients with recent myocardial infarction.[21]

2) Hypertension

In hypertension heart rate and blood pressure are increased in the early morning hours (morning or a.m. Surge). The blood pressure increases from midafternoon and is minimum at midnight. In mostly high blood pressure patients, there is a rather distinct rise in blood pressure upon awakening that is called the morning or ―a.m. the systolic blood pressure rises approximately 3mm hg/hour for the first 4-6 hours post-awakening, while the rate of increase of diastolic blood pressure is approximately 2mm hg/hour.[22]

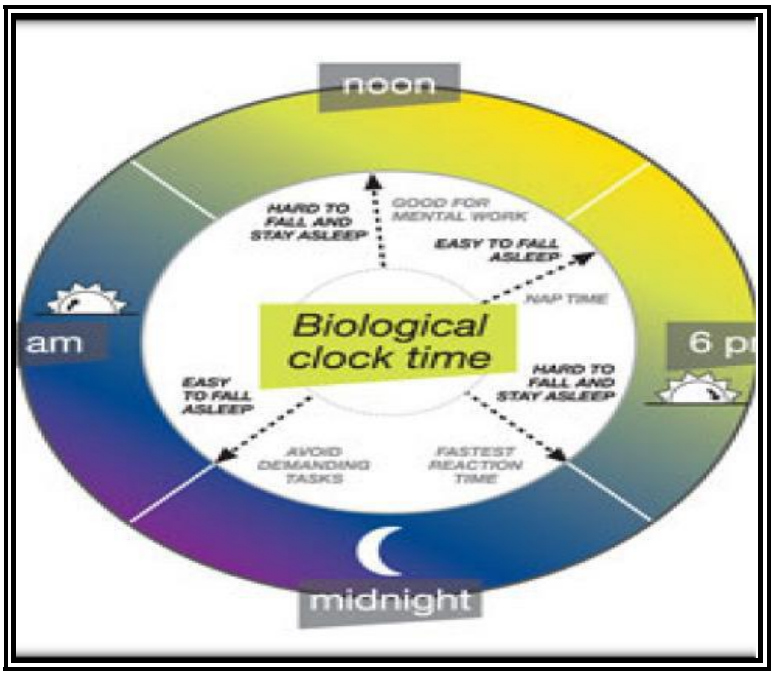

Fig. 7: Biological clock time for chronobiology.

3) Neoplastics

Antineoplastic drugs cause cytotoxic effects on healthy and diseased tissues. As would be predicted that, the biological rhythms of both healthy and tumor cells may influence the susceptibility of normal and malignant cells to these agents. It has been confirmed that susceptibility rhythms to drugs may differ between healthy tissue and cancerous tissue. Therefore, the correct timing of drug treatment may reduce host toxicity, increase the maximum drug tolerance, and ultimately result in better tumor management.[23]

4) Peptic Ulcer Disease

Peptic ulcer is because of maximal acid secretion the peptic ulcer disease pain and perforation of gastric and duodenal ulcers are more frequent at night, administration of drugs at bedtime is more efficient in peptic ulcer disease. Nocturnal administration not only reduces acid secretion more effectively but also promotes ulcer healing and reduces ulcer reappearance. Bedtime h2-receptor blockade is one such regimen used for peptic ulcer disease.[23]

5) Myocardial Infarction

Occurrence of myocardial infarction has been shown to be more frequent in the morning .in which 34% events occurring between 6 a.m. And noon. Acute cardiac arrest and transient myocardial ischemia shows an increased frequency in morning. The causes for these findings have been suggested to be release of catecholamine, Cortisol increase in the platelet

aggregation and vascular tone. ACE inhibitors shows greater results when they are administered during night. Atenolol, Nifedipine and Amlodipine are more effective when administered at night.[24]

6) Duodenal Ulcer

Many of the functions of the gastrointestinal tract are subject to circadian rhythms. Like gastric acid secretion is highest at night, while gastric and small bowel motility and gastric emptying are all slower at night. These biorhythms have important implications in the pharmacokinetics of orally administered drugs. At nighttime, when gastric motility and emptying are slower, drug disintegration, dissolution, and absorption may be slower. In peptic ulcer patients, gastric acid secretion is highest during the night. Suppression of nocturnal acid is an important factor in duodenal ulcer healing. Therefore, for active duodenal ulcer, once daily dosage regimen of H_2 antagonist at bedtime is the recommended for better implication. The theoretical problems which associated with a sustained or profound decrease of 24-h intra gastric acidity include the threat of enteric infection and infestation, potential bacterial overgrowth with possible n-nitrosamine formation, drug-induced hyper gastrinaemia and disturbed protein digestion. In night when these types of potential problems occurs. That time the management of simple peptic ulceration is necessary, it appears sensible to use and the minimum intervention required. For such a reason administration of h2-receptor blockade at bedtime is give effective result.[24]

7) Arthritis

The patients suffering from osteoarthritis are reported to have less pain in morning hours as compared to night, while patients suffering from rheumatoid arthritis feel more pain in the morning hours than nights. In this case taking medication at night is an apparent solution. NSAID such as Ibuprofen need to be administered 4 to 6 hours before achieving their maximum benefit, as a result peak will occur at patients waking and the effect will be decline as patient start to wake up. There is circadian rhythm in the plasma concentration of c reactive protein and interleukin – 6 of patients with rheumatoid arthritis.[25]

8) Hypercholesterolemia

Hypercholesterolemia is the diverse directions of circadian changes in lipid fractions. In patients and normal subjects may contribute to alteration in the rhythm city of other metabolisms and in the blood coagulation system, thus leading to various complications a circadian rhythm occurs during hepatic cholesterol synthesis. However, this rhythm varies

according to individuals. Indeed, there is a large variation in plasma mevalonate concentrations between individuals. Therefore cholesterol synthesis is generally higher during the night than during daylight, and diurnal synthesis may represent up to 30%–40% of daily cholesterol synthesis many individuals display a paradoxical synthesis, with an inverted diurnal cholesterol synthesis. It seems therefore that cholesterol is synthesized during the night as well as during daylight or however it is higher in night. However the maximal production occurs early in the morning, i.e. 12 h after the last meal. studies with 3-hydroxy-3-methylglutaryl-coenzyme (HMGCoA) inhibitors have suggested that evening dosing was more effective than morning dosing.[25]

9) Bronchial asthma

Asthma is a chronic inflammatory disease of the airways, which characterized by hyper responsiveness to a variety of stimuli. The role of circadian rhythms in the pathogenesis and treatment of asthma indicates that, airway resistance increases gradually at night in asthmatic patients. Circadian changes are seen in normal lung function, which reaches a low point in the early morning hour's. the worsening of asthma at night, commonly referred to as nocturnal asthma (Na). A drug delivery system which administered at bedtime but releasing drug during morning hours such type of system would be ideal in this case18asthma is the most common disease in which the large circadian variation occurs with respect to time. The symptoms of asthma occur 50 to 100 times more at night. The exacerbation of asthma during the night represents the changing status of biological functioning due to circadian rhythms in bronchial patency. their ways hyper reactivity increases due to acetylcholine, histamine, and house dust as well as plasma cortisol, epinephrine, histamine, and cyclic Amp. Once daily dosing of inhaled glucocorticosteroidciclesonide, sustained release theophylline, transdermal tulobuterol patch found to be effective incase of nocturnal asthma.[26]

10) Diabetes

The circadian variations of glucose and insulin in diabetes have been extensively studied. The goal of insulin therapy is to mimic the normal physiologic pattern of endogenous insulin secretion in healthy individuals, with continuous basal secretion as well as meal stimulated secretion.

Table no 2: List of the marketed chronopharmaceutical dosage forms and the pulsatile drug delivery technologies used.

Registered trade mark ®	Drug	Chronopharmaceutical Technology®	Drug release mechanism	Timing of drug administration	Indications for chronotherapy
Cardizem La	Dilitiaze M hcl	Ceform Microsphere Technology	Diffusion/ Erosion	Bedtime	Hypertension
Aciphex	Rabeprazole sodium	Enteric Coating Technology	Delayed-Release	After Morning Meal	Healing Of Duodenal Ulcers
Cardura Xl	Doxazos In Mesylate	Oros Technology	Osmotic Regulation	Administer Ed With Breakfast	Benign Prostatic Hyperplasia

Table no.3: List of the chronopharmaceutical dosage forms marketed and the pulsatile drug delivery technologies used.

Registered trade mark ®	Drug	Chronopharmaceutical Technology®	Drug release mechanism	Timing of drug administration	Indications for chronotherapy
Dexilant	Dexlansopra Zole	Ddr Technology	Dual Drug Release	Fasting State Before Breakfast	Healing Of Erosive Esophagitis
Diamicron Mr.	Gliclazide	Hydrophilic Matrix Technology	Swelling, Diffusion, Erosion	Breakfast Time	Type II Diabetes
Glucotrol Xl	Glipizide	Oros Technology	Osmotic Regulation	Morning	With Food Type II Diabetes
Ditropan Xl	Oxybutynin Hcl	Oros Technology	Osmotic Regulation	Morning	Urinary Incontinence

Table no 4: List of the chronopharmaceutical dosage forms marketed and the pulsatile drug delivery technologies used.

Registered trade mark®	Drug	Chronopharmaceutical Technology ®	Drug release mechanism	Timing of drug administration	Indications for chronotherapy
Coruno	Molsidomi Ne	Geomatrix Technology	Swelling, Gelling, Erosion	Morning	Chronic Angina Pectoris
Covera-Hs	Verapamil Hcl	Oros Technology	Osmotic Regulation	Bedtime	Hypertension
Lodotra	Prednisone	Geoclock (Geomatrix) Technology	Delayed-Release/ Immediate-	Bedtime (4 H After Ingestion)	Rheumatoid Arthritis

			Release		
Coreg Cr	Carvedilol Phosphate	Micro pump Platform	Immediate-Release/ Controlled-Release	Morning With Food	D Heart Failure, Heart Attack, Hypertension

MICROMERITIC PROPERTIES

1. Bulk density, tap density

Bulk density is defined as the mass of a powder divided by the bulk volume. The bulk density of a powder depends primarily on particle size distribution, particle shape, and the tendency of the particles to adhere to one another. A quantity of accurately weighed powder (bulk) from each formula, previously shaken to break any agglomerates formed was introduced into a 10 ml measuring cylinder. After the initial volume was observed, as bulk volume. The cylinder was introduced onto a hard surface of holly instrument. After that The Bulk and Tap densities, Haussner's ratio and Carr's Index were calculated. Each micrometric property was performed in triplicate manner and reported.[27]

2 Carr's index

The compressibility index of the granules was determined by Carr's compressibility index. (%) Carr's Index can be calculated by using the following formula,

$$\textbf{Carr's index} = \frac{Tapped\ density - Bulk\ density}{Tapped\ density} \times 100$$

Table no. 5: Grading of the powders for their flow properties.

Sr.no.	Consolidation index (Carr's index %)	Flow
1	5-15	Excellent
2	12-16	Good
3	18-21	Fair to Passable
4	23-35	Poor
5	33-38	Very Poor
6	>40	Very Very Poor

3. Hausner's ratio

Hausner's Ratio of powder was determined by comparing the tapped density to bulk density using the equation.[28]

$$\textbf{Hausner's ratio} = \frac{Bulk\ density}{Tapped\ density} \times 100$$

4. Determination of angle of repose

The flow ability was determine by the angle of repose () using fixed funnel method. Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and horizontal plane. Angle of repose has been used as indirect methods of qualifying powder flow ability, because of their relation with inter particular friction. The frictional force in a loose powder can be measured by angle of repose.[29]

Formula for calculating angle of repose given as follows

Tan θ=$\frac{h}{r}$

Θ= tan-1 (h/r)

Where, Θ is the angle of repose

H is height of pile

R is radius of the base of pile

Table no 6: Different ranges of flow ability in terms of angle of repose.

Sr. No.	Flow Property	Angle of Repose (degrees)
1	Excellent	25-30
2	Good	31-35
3	Fair-aid not needed	36-40
4	Passable-may hang up	41-55
5	Poor-must agitate, vibrate	46-55
6	Very poor	56-65
7	Very, very poor	>66

EVALUATION PARAMETER OF TABLET

1. Uniformity of thickness

The thickness of individual tablet may be measured with a micrometer, which permits accurate measurements and provides information on the variation between tablets. The thickness of a tablet is determined by the diameter of die, the amount of fill permitted to enter the die, the compaction characteristics of the fill material, and the force or pressure applied during compaction. The tablet thickness was measured using Vernier caliper.[30]

2. Hardness test

Tablets require a certain amount of strength, or hardness and resistance to friability, to withstand mechanical shocks of handling in manufacture, packaging and shipping. In addition, tablet should be able to withstand reasonable abuse when in hands of consumer. The relationship between hardness to disintegration and perhaps to drug dissolution release rate

has become apparent. The hardness of tablet was determined using apparatus Pfizer Hardness tester. It is expressed in kg/cm2. Five tablets were randomly selected from each formulation and the mean and standard deviation values were calculated.[31]

3. Friability test

It is the phenomenon whereby tablet surfaces are damaged and/or show evidence of lamination or breakage when subjected to mechanical shock or attrition. The friability of tablets was determined by using Roche Friabilator. It is expressed in Percentage (%). Ten tablets were initially weighed (W initial) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100revolutions. The tablets were weighed again. (W final). The percentage friability was then calculated 31by using following formula

$$F=\frac{W\ initial-W final}{W\ initial}\times 100$$

% Friability of tablets less than 1% is considered acceptable

4. Weight variation test

The weight variation test would be a satisfactory method of determining the drug content uniformity of tablets if the tablets were all or essentially all (90 to 95%) active ingredients, or if the uniformity of drug distribution in the powder from which tablets were made perfect. Ten tablets were taken and their weight was determined individually and collectively by using single pan electronic balance. The average weight of the tablets was determined from collective weight. From the individual tablets weight, the range and percentage standard deviation was calculated. Not more than 2 tablets should deviate from the average weight of tablets and the maximum percentage of deviation allowed. In direct compression of tablet, uniform weight of tablets represents appropriate powder flow and uniform die filling.[32, 33]

Table no 5: Weight variation test limit as per USP.

Average weight of a tablet	Percentage deviation
30 mg or less	10%
More than 130 mg and less than 324 mg	7.5%
324 mg or more	5%

5. Drug content uniformity

The tablets were randomly selected from each batch of formulation and subjected for content uniformity test. The tablets were taken and milled separately by using glass mortar and pestle then powder equivalent to 10 mg of drug were accurately weighed and transfer 50 ml of 0.1N HCL solution and stir to mix properly. Resulting solution was filter through whatmman filter

paper and the final volume adjusted with 0.1N HCL up to 100ml. Then the suitable dilutions were prepared and samples were analyzed by using validated UV Visible Spectrophotometer (Agilent Technologies Cary 60 UV-Visible double beam spectrophotometer) at 214 nm using 0.1N HCL as blank.[34]

6. In-vitro disintegration time

The process of breakdown of a tablet into smaller particles is called as disintegration. Disintegration of tablet was generally occurring due to water uptake by tablet via capillary action, which results in swelling, and thus tablet get disintegrated. It was also reported that increased compaction force may increase or decrease disintegration time. In the present study disintegration test was carried out on six tablets using the apparatus specified in IP (disintegration apparatus IP). The phosphate buffer at 37^0C ± 2^0C was used as a disintegration media and time in minute taken for complete disintegration of the tablet with no mass remaining in the apparatus was measured.[35]

7. In-vitro dissolution studies

In-vitro dissolution study of CT and Pulsatile Tablet was carried out using VDA-8DR, USP, Veego dissolution test apparatus.[36, 37]

I) In-Vitro Dissolution Study of Core Tablet (CT)

Tablet was introduced into the basket of the Electro lab TDT- 08L USP dissolution test apparatus and the apparatus was set in motion, and rotated with 100 rpm and 5ml of sample was withdrawn for first half hour at 5 min intervals. And dilute to 10ml with 0.1 N HCl. Samples withdrawn were analyzed by UV spectrophotometer for presence of drug using 0.1N HCL solution as blank.

Table no 6: General dissolution conditions for core tablet (ct).

Sr. No.	Parameter	Specification
1	Dissolution medium	900 ml of 0.1N HCL
2	Temperature	37^0±0.5^0
3	Rotation Speed	75 RPM
4	Volume Withdrawn	5ml
5	Λ max	214
6	Time Interval	5 min
7	Beer's range	5-25µg/ml

II. In-Vitro Dissolution Study of Pulsatile Release Tablet (PRT)

Different coating compositions were evaluated for providing pulsatile drug delivery of Quinapril Hydrochloride. Initially Tablets were coated with HPMC K4M, HPMC K100M and EC as well as spray dried lactose and magnesium stearate are used for compressed coating tablets. And form pores through which buffer Penetrate in EC coated layer. Because of the penetration of the buffer into inner coating layer, HPMC of inner coating layer swells and it ruptures the EC coated layer and drug release takes place after 8 hr. HPMC coated tablets were coated with different proportion of Ethyl cellulose.

Table no 7: Summary of general dissolution conditions pulsatile release tablet (prt).

Sr. No.	Parameter	Specification
1	Dissolution Medium	900 ml of 0.1NHCL
2	Temperature	$37^0 \pm 0.5^0$c
3	Rotation Speed	75RPM
4	Volume Withdrawn	5 ml
5	Time interval	1 hrs
6	Max	214
7	Beer's range	5-25 µg/ml
8	Dilution factor	2 ml

8. In-Vitro Buoyancy Studies

The time between introduction of dosage form and its buoyancy on the simulated gastric fluid and the time during which the dosage form remain buoyant were measured. The time taken for dosage form to emerge on surface of medium called floating Lag Time (FLT) or Buoyancy Lag Time (BLT) the in-vitro buoyancy was determined by floating lag time as per the method described .The tablets were placed in a 100 ml glass beaker containing simulated 0.1N Hydrochloric acid, as per USP. The time required for the tablet to rise to the surface and float, was determined as the floating lag time.[38]

9. Total Floating Time (TFT)

The duration of time at which the dosage form constantly remained on the surface of medium was determined as the total floating time (TFT). The Total Floating Time was determined by as per the method described. The tablets were placed in a 100ml glass beaker containing simulated 0.1N Hydrochloric acid, as per USP. And Time when the tablet burst and core tablet is out of press coating. This is considered as predetermined off-release period .that is total floating time.[39]

10. Effect of Outer Polymer Concentration and Water Uptake Performance

To study the effect of outer polymeric layer concentration on lag time, core tablets were coated with different levels of Ethyl cellulose, HPMC, Lactose spray dried and magnesium stearate. The % water uptake capacity of tablets (wo) was determined before the test, and then the tablet was put into the basket and immersed in 900 ml phosphate buffer. The basket was rotated at 100 rpm in the dissolution apparatus. Tablets were removed from containers at predetermined regular intervals, blotted with tissue paper, weighed (wt). The % water uptake was calculated using the formula,[40]

$$\%\text{Water uptake}=\frac{wt-wo}{wo}\times 100$$

REFERENCES

1. C. R. Matholiya., A. S. Dedakia. An Approach For Controlled Drug Delivery. As Pulsatile Drug Delivery System. International Bulletin 0f Drug Research, 2(3): 1-21.
2. T.B.Kakade, D.B.Shelar, S.S.Tikole, G.S.Bamane, A.T.Ubale; Floating Pulsatile Drug Delivery System. International Research Journal for Invention in Pharmaceutical Sciences, 2014; 2321-7855.
3. Davis S.S., Illum L., "Drug delivery system for challenging molecules". Int. J.pharm., 1998; 176: 1-8.
4. Survase S and Kumar N. Pulsatile drug delivery: Current scenario; CRIPS, 2007; 8(2): 2.
5. Anal AK. Time-controlled pulsatile delivery system for bioactive compounds. Recent Patents on Drug delivery and formulation, 2007; 1: 73- 79.
6. Lavanya M, Jayanth P, Datta D, Niranjan Babu M, Gastroretentive Drug Delivery System; Indo American Journal of Pharmaceutical Research, 2013; 3(9): 7307-7315.
7. V. P. Patel., T. R. Desai., C. R. Matholiya., A. S. Dedakia. Pulsatile Drug Delivery System: A Review 1-32.
8. S. Patel., M.K.Modasiya., V.M.Patel., A.K.Patel. Design and Development Of Floating Pulsatile Drug Delivery System Using Meloxicam. International Journal of Pharmaceutical Research And Bio-Science, 2012; 1(2): 215-235.
9. G. Pragna., B. Shravani., N. G. Raghavendra Rao., Pulsatile Drug Delivery System: An Overview International Journal Of Pharmaceutical Development And Technology, 2013; 3: 97-105.
10. V. V. Prasanth., M.P. Modi., S. T. Mathew. Pulsatile: A Tool For Circardian Rhythm - A Review. Journal Of Drug Delivery & Therapeutics, 2012; 2(1): 58-65.
11. N. G. Raghavendra Rao., P. Soumya., K. Revathi., B. S. Nayak A Review On Pulsatile

Drug Delivery System. International Research Journal Of Pharmacy, 2013; 4(3): 31–44.

12. S. R. Patel., A. K .Patel. M. K. Modasiya., V. M .Patel, Journal Of Pharmacy Research, 2012; 5(4): 2264-2271.
13. G. N. Bharti., P. Sharma., N. Bhandari, K. Singh., A .Kumari . Pulsatile Drug Delivery as Modified Release Dosage Form: A Review. Journal Of Drug Delivery & Therapeutics, 2012; 2(6): 102-110.
14. M. Kaur And R. Bala. Chronotherapy: A Review International Journal of Pharmaceutical Sciences and Research, 2013; 4(1): 90-102.
15. J. Rk. Reddy., M.V. Jyothsna., T. S .Mohamed Saleem. C.Ms. Chetty. Review On: Pulsatile Drug Delivery Systems. Journal of Pharmaceutical Sciences and Research. 2009; 1(4): 109-115.
16. C. Bobade., A. Kulkarni And V. Chaudhari. A Review On Types And Methodologies Of Pulsatile Drugdelivery System International Journal Of Pharmaceutical And Chemical Sciences, Jul-Sep 2012; 1(3): 923-932.
17. G. S. Sharma., M.V. Srikanth., M .U. Uhumwangho., K.S. Phani., And K. V . Ramana Murthy .Recent Trends In Pulsatile Drug Delivery Systems - A Review International Journal Of Drug Delivery, 2010; 2: 200-212.
18. C .R. Matholiya, A. S. Dedakia. An Approach For Controlled Drug Delivery: As Pulsatile Drug Delivery System International Bulletin Of Drug Research, 2(3): 1-21.
19. www.pharmatutor.org/articles/review-overview-floating-drug-delivery-system?page=1
20. C.R. Matholiya., A. S. Dedakia An Approach For Controlled Drug Delivery: As Pulsatile Drug Delivery System International Bulletin Of Drug Research, 2(3): 1-21.
21. V. S. Chhabra., S. K. Tilloo., S. R. Walde., A. M. Ittadwar. The Essentials Chronopharmacotherapeutics International Journal of Pharmacy and Pharmaceutical Sciences, 2012; 4(3): 2012.
22. D. K. Singh., A.S. Poddar, S.U. Nigade, S. S. Poddar., Pulsatile Drug Delivery System: An Overview. International Journal Of Current Pharmaceutical Review And Research, May-July 2011; 2(2): 1-8.
23. B. Maunitkumar, S.V. Mehta, M.M. Nathwani, Soniwala., Pulsatile Drug Delivery System: Advanced And Novel Approach Mintage Journal Of Pharmaceutical And Medical Sciences, Feb 2014; 3(1): 4-11.
24. S. Y. Lin., Y. Kawashima., Current Status And Approaches To Developing Press-Coated Chronodelivery Drug Systems. Journal Of Controlled Release, 2012; 157: 331–353.

25. D. Jain, R. Raturi, V. Jain., P. Bansal And R. Singh., Recent Technologies In Pulsatile Drug Delivery Systems. Biomatter, July/August/September 2011; 1: 1-9.
26. H. Zou, X. Jiang, L. Kong. And S. Gao. Design And Gamma-Scintigraphic Evaluation Of A Floating And Pulsatile Drug Delivery System Based On An Impermeable Cylinder. Chem. Pharm. Bull, 2007; 55(4): 580-585.
27. S. Bhanja., D. K. Hardel., M. Sudhakar., Formulation And Evaluation Of Mouth Dissolving Tablets Of Quinapril hydrochloride. International Journal Of Current Pharmaceutical Research, 2012; 4(4): 15-23**.**
28. K. Thalberg, D. Lindholm, A. Axelsson, Comparison of Different Flowability Tests for Powders for Inhalation. Science Direct. Powder Technology, 2004; 146: 206–213.
29. K.E. Ileleji, B. Zhou, The Angle Of Repose Of Bulk Corn Stover Particles. Science Direct. Powder Technology, 2008; 187: 110–118.
30. R. Gollapudi., H. Javvaji., R. Rao., Tadikonda., And V. Arpineni., Formulation And In Vitro Evaluation Of Sustained Release Matrix Tablets Of Quinapril hydrochloride. An International Journal Of Advances In Pharmaceutical Sciences, 2011; 2(1): 31-36.
31. S. Lingaraj, Danki, U.Reema, S. Maind, S. A. Raju M. P. Reddy., Development and in Vitro Evaluation of Gastroretentive Drug Delivery System of Quinapril hydrochloride. Scholars Research Library, 2011; 3(3): 1-22.
32. Weight Variation Of Dietary Supplements 2091.Usp Official Pharmacopoeial Test.
33. H. Liberman, L. Lachman, The Theory And Practice Of Industrial Pharmacy, 3rd Edition, Varghese Publication House, 1991; 171-193.
34. P. K. Lende, M. S. Junagade, A. D. Deshmukh, Formulation Optimization And In Vitro Evaluation Of Floating Tablet Stavudine Ameriacan Journal Of Pharmatech Research, 2012; 2(5): 724-738.
35. A. Martin, Micromereteics Physical Pharmacy. Baltimores, MD: Lippincott Williams And Wilkins, 2001; 423-454.
36. E. Aultan Pharmceutics, The Science Of Dosage Form. Second Edition, Churchil Livingstone, 2002; 397-439.
37. US-FDA Dissolution Methods For Drug Products. Http://Www.Accessdata.Fda.Gov/Scripts/Cder/Dissolution/Dspsearchresultsdisso Lutions.Cfm, 2008.
38. P. V. Shind, R .V. Mayee., Evaluation Of Floating Press-Coated Pulsatile Release Of Aceclofenac Tablets. A Solution For Rheumatoid Athrites. Asian Journal of Biomedical and Pharmaceutical Science, 2013; 3(17): 16-21.

39. B.C. Shekar., R.S. Kiran., B. N. Babu Preparation And Evaluation Of Gastro Retentive Floating Tablets Of Ketoconazole International Journal Of Pharma Research And Development, Nov 2010; 2(9): 174-184.
40. Y.S. Tanwar, M. Jamini, and B. Srivastava., Formulation And In Vitro Evaluation Of Floating Tablets Of Quinapril hydrochloride. Mahidol University Journal of Pharmaceutical Sciences, 2013; 40(2): 17-24.