International Journal of Pharmaceutical Research and Applications
Volume 5, Issue 2, pp: 441-448 www.ijprajournal.com ISSN: 2249-7781

Recent Review on Pulsatile Drug Delivery System (Pdds) Technologies for Future Advantages: A Review.

Meghana Solanki [1*], Prof. Bhavna Joshi[2], Dr. Umesh Upadhyay[3].
[1]7th semester B. pharm, Sigma Institute of pharmacy, Bakrol, Ajwa, Vadodara – 390019 (Gujarat, India).
[2]Associate Professor, Sigma Institute of pharmacy, Bakrol, Ajwa, Vadodara – 390019 (Gujarat, India).
[3]Principal, Sigma Institute of pharmacy, Bakrol, Ajwa, Vadodara – 390019 (Gujarat, India).

Date of Submission: 1-11-2020 Date of Acceptance:15-11-2020

ABSTRACT: The release of drug in an immediate or extended release both is easy with palatial drug delivery system. This system of drug release is having advantages to easily reach blood circulation. In this delivery of drug are sensitive to stimuli and external environment "Define as system where drug is release suddenly after a well defined lag time according to the circadian rhythm of the disease". Dosage forms are coated by polymer to achieve the colon target drug delivery system can attuned by this delivery system. Pulsatile drug delivery system (PDDS) has developed because of their multiple advantages over conventional dosage forms. Hold good promises of benefit to the patients suffering from chronic problems like arthritis, asthma, and hypertension. Marketed technologies, such as PulsicapTM, Diffucap, CODAS, OROS and PULSYSTM are available.

Keywords: PDDS (Pulsatile drug delivery system), circadian rhythm, Chronological behavior, lag time, controlled release, chronic problem.

I. INTRODUCTION

Release of drug in an immediate or extend both are easy with PULSATILE DRUG DELIVERY SYSTEM.

They are predictable resonating dynamic systems, which require different amount of a drug at predictably different time within the circadian cycle which will maximize desired and minimize undesired drug effect [1,2]. System where drug is release suddenly after a well-defined lag time according to the circadian rhythms of the disease.

However, there is certain condition for which such release pattern is not suitable. This condition demand release of drug after lag time .in other words, it is required that the drug should not be release at all during the initial phase of dosage form administration. such a release pattern is known as palatial drug delivery system.[3]

This technical gaining a lot of inters as the deliver the drug at the right placemat the right time and in right amount, so this system increases patient compliance. This system of drug release is having advantage to easily reached blood circulation. dosage forms are coated by polymer to achieve the Colon targets drug delivery system.

Many advantages are available with help of PDDS including reduction in dose of drug, reduce dosage frequency, drug fluctuating is available. Many diseases are hypercholesterolemia, asthma, cancer, duodenal ulcer, arthritis, neurological disorders, cardiovascular disease, colonic delivery are easy to improve by help of palatial drug delivery system.[4]. They are predicted resonating dynamic system, which required different amount of a drug at predictably different time within the circadian cycle which will maximize desired and minimize undesired drug effect [5,6].

II. METHODS:

In PDDS different type are available.

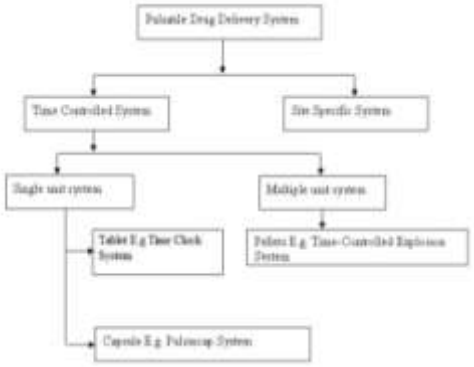

Figure1. classification of PDDS [7].

International Journal of Pharmaceutical Research and Applications
Volume 5, Issue 2, pp: 441-448 www.ijprajournal.com ISSN: 2249-7781

1) Time control pulsatile system:

Time control palatial system can be categorizing in single unit & multiple unit system. In time control drug delivery system release exists after lag time or at specific time.

A) Single unit pulsatile system.

a) Capsular system: In capsular system release of drug are controlled according to time specification. The generally contain two or more layers are designed. Which one is immediate release and second are have enlarge release.

Capsule contain body and cap, release controlling plug between immediate release compartment and pulse release compartment. On contact with aqueous fluid, the cap rapidly dissolves than releasing the immediate release component followed by pulsed release component [8,9].

b) PORT (Pediatric oncology resource team) system: In this system an implanted part catheter system is a catheter that is introduce in obtrusive and cagily accessible area of the body under the skin. E.g. chest areas.

c) Based on osmotic pressure: Osmotic ally control system: in this system drug / active ingredients are coated by polymer membrane which can affect by osmotic pressure .and they make a reservoir type or matrix system and then drug is release. The system showed good correlation in lag times of in vitro -in vivo experiment in humans [10].

d) Based on solubility modification: This system specially developed for delivery of Salbutamol sulphate [11]. Salbutamol has solubility of 275 mg/ml in water and 16mg/ml in saturated solution of NACL. Release of API are possible in suitable solubility which can enhanced with help of polymers.

e) Reservoir system: Palatial drug delivery system which are tablet can be prepare by using double layer system. in this first layer composed of polymer they come contact with body fluid than convert in to reservoir type and then release of API.

B) Multiple unit system: Multiple units consists multiple small unit which all are important and have specific effect at site of action.

a) Reputable coating system: Administration of drug is affect by various types of factor. But now we can administer the drug with help of coating materials which will be reputable and follow release of drug by matrixes type system.

b) Time controlled explosion system: In this system drug release are possible based on osmotic and swelling effects. the core contains the drug a low bulk density solid and /or liquid lipid material (e.g. mineral oil)& disintegrate [4].

c) Modifies permeation system: Modification in permeation of body fluid in the dieses and follow drug release. Here, permeation of body fluid or water are reduce or make time consuming by help of polymer or we can use water insoluble polymer e.g. polyvinyl formal (PVF), Polyvinyl acetate (PVAC).

2) Stimuli induced:

1) Thermo responsive: Some drug widely sensitive to thermal response. We can administer the drug in inactive form and they are activating by giving the thermal energy at the time of action.

2)Chemically stimuli induced: In our body various chemical changes occur and in these circumstances the drug release & their action and efficacy are also affect and alter. Here, we can administer the drug safe from chemical changes.

a) Glucose sensitive system: In the diabetes condition there increases the level of glucose in the body. At the time required the inject of insulin at right time. developed glucose sensitive system which are release the insulin as per body need are maintain.

One such system includes PH sensitive hydrogen containing glucose oxidizes glucose in immobilized in the hydrogen [4].

Examples: N, N-dimethylaminoethyl methacrylate, chitosan. [12,13].

b) PH based system: In this type of drug delivery system the drug are having different types of pulsed release are available when drug release by changes in PH they called PH based drug delivery system. In stomach and GIT have various in PH levels. We can protect out the drug from different level of PH with help of polymer coating which are not affected by upper stomach PH and drug reach Colon target release.

International Journal of Pharmaceutical Research and Applications
Volume 5, Issue 2, pp: 441-448 www.ijprajournal.com ISSN: 2249-7781

Figure2. Pulsincap release [14].

Example: - PH dependent polymer is cellulose acetate phthalate polyacrylates. this polymer is used as enteric coating material so as to provide release of drug in the small intestine [15].

3) External stimuli: Various External factors can affect the drug release. include moisture, magnetic fold, temperature, electric response.

a) Elect responsive palatial system: This type of response in which polymer contains higher concentration of ionizable group. This ionizable group activates by giving the electric field and they give release as per body need.
Natural polymer: - Carbomer, agarose, Xanthan gum.
Synthetic polymer: - Generally acrylate & methacrylate derivatives such as partially hydrolyzed polyacry lamide, polydimethy laminopropy l acrylamide [16].
b) Magnetic responsive palatial system: - Same as Elect responsive system but here give the magnetic fields and polymer are used which have high concentration of magnetically active polymer. Ex: Ferric oxide.

Nan composites hydrogen are one types of on-off device where drug release can be turn on by application of alternative magnetic field. [17].

Biological rhymes [18].
1. Ultradian Rhythms:

Oscillations of shorter duration are termed Ultradian Rhythms (more than one cycle per 24h). E.g.90 minutes sleep cycle.

2. Infradian Rhythms:

Oscillations that are longer than 24 hours are termed as Infradian Rhythms (less than one cycle per 24 hours) E.g. Monthly Menstruation.

3. Circadian rhythms:

Circadian rhythms are self-sustaining, endogenous oscillations

Figure 3. CIRCADIAN RTYTHM CYCLE.[20].

Diseases That Are Pushing The Requirements Of Pulsatile Drug Delivery System:

Many dieses like cardiovascular disease asthma, arthritis, duodenal ulcer, cancer, hyper cholesterolemia, diabetes.

1) Cardiovascular disease: -- In cardiovascular disease capillary resistance and vascular reactivity are higher in then cardiovascular disease capillary resistance and vascular reactivity is higher in the morning and decrease latter in the day. Platelet agreeability is increased and fibrinolytic activity is decrease in the morning, leading to a state of relative hypercoagulability of the blood. [19]. This alterations is affected by altered various external factors. Trial arrhythmias appear to exhibit circadian pattern usually with a higher frequency in the day time and lower frequency in the night time with the abnormal foci under the same long-terms autonomic regulation as normal pacemaker tissue [21,22].

2) Asthma: In asthma airways resistance increase at night in asthmatic patient. Followed reach a low point in early morning. this is appeared in people with asthma. Chronotherapies have been studied for asthma with oral corticosteroid, theophylline and B2-agonists [23,24]. Approximately two-thirds of asthmatics suffer from night-time symptoms. Lung function is usually highest at 4 PM and lowest at 4 AM. [25].

International Journal of Pharmaceutical Research and Applications
Volume 5, Issue 2, pp: 441-448 www.ijprajournal.com ISSN: 2249-7781

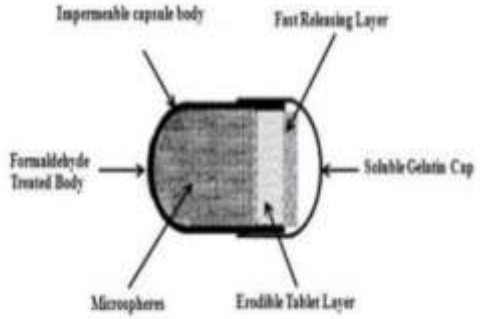

Figure 4. ASSEMBLY OF PDDS CONTAINING GLIPIZIDE USED IN ASTHMA. [26,27].

3) Arthritis: Chronotherapy for all forms of arthritis using NSAIDs such as ibuprofen should be timed to ensure that the highest blood level of the drug coincide with peck pain [16]. the same drug would be more affective for people with rheumatoid arthritis when taken after the evening meal [28,29]. dose depend on severity of pain and patient physiology.

4) Duodenal ulcer: Circadian rhythm are subject in GIT and affect the function of GIT, gastric acid secretion are higher at night, and motility of Small bowel and emptying are slower, so these affect the drug disintegration, dissolution & absorption are reduce. In these rhythms higher acid secretion are the needs to increase the PH of GIT in ulcerative condition. Therefore, for active duodenal ulcer, once daily at bedtime is the recommended dosage regimen for H2 antagonist [30].

5) Cancer: Circadian rhythmic changes are affecting the growing the tumor cell. circadian rhythm changes in tumor blood flow and cancer growth, when tumors are small and growing most rapidly and when they larger and growing more slowly. The Chronotherapy concept offers further promise for improving current cancer treatment options, as well as for optimizing the development of new anticancer or supportive agent [31,32].

6) Diabetes: Circadian rhythm is also affecting the secretion of insulin. Providing basal insulin exogenously to patient with diabetes inhibits hepatic glucose production [31,32].

7) Hypercholesterolemia: Circadian changes diverse the lipids fraction they may contribute alterations in other metabolism and blood coagulation. Therefore, cholesterol synthesis is generally higher during the night than during daylight, and diurnal synthesis [33]. Studies with HMGCOA reeducates inhibitors have suggested that evening dosing was more effective than morning dosing [34].

Disease	Chronological behavior	Drug used
Peptic Ulcer	Acid secretion is high in the afternoon and at night	H_2 blockers
Asthma	Precipitation of attacks during or at early morning hour	β_2 agonist, Antihistaminics
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 etc
Arthritis	Pain in the morning and more pain at night	NSAIDs, Glucocorticoids
Diabetes Mellitus	Increase in the blood sugar level after meal	Sulfonylurea, Insulin, Biguanide
Attention deficit syndrome	Increase in DOPA level in the afternoon	Methylphenidate
Hypercholesterolemia	Cholesterol synthesis is generally higher during night than during day time	HMG CoA reductase inhibitors

Table1: TABLE OF DRUG, CHRONOLOGICAL BEHAVIOR & USES OF DRUG. [33]

III. MECHANISMS OF DRUG RELEASE FROM PULSATILE DRUG DELIVERY SYSTEM.

1)Diffusion: Drug comes contact with aqueous fluid in gastrointestinal tract (GIT), water part of GIT fluid is diffusing into the particle of drug. dissolution of drug start and the drug solution are diffuse across the release membrane to the exterior.

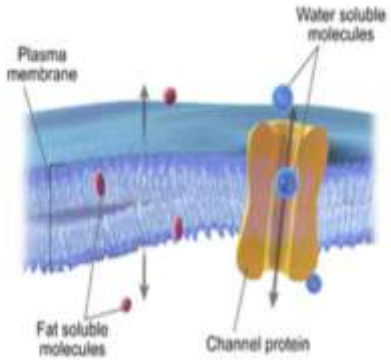

Figure5. diffusion across the cell [35].

2) Erosion: Some polymers are coating can be designed to erode gradually with time, thereby releasing of the drug across the membrane by erosion of membrane.

3) Osmosis: In allowing water to entre 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 [19].

International Journal of Pharmaceutical Research and Applications
Volume 5, Issue 2, pp: 441-448 www.ijprajournal.com ISSN: 2249-7781

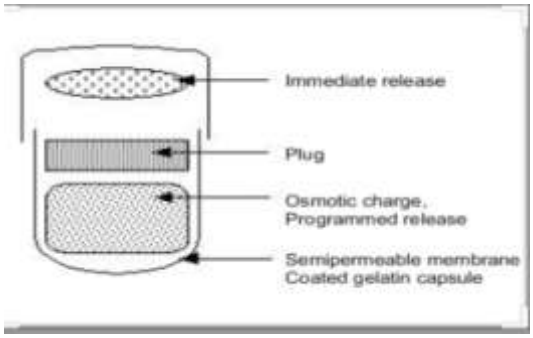

Figure 6. Osmotic release [36].

Advantages:

1) Activity extended day time night time.
2) Side effects are reducing.
3) Improve patient compliance.
4) Reduce dose frequency.
5) Colon targeted administration of drug are possible.
6) Protecting mucosa from irritations.
7) Reduction in dose size.
8) Drug loss is preventing by extensive first passed metabolism.

Disadvantages:

1) Low drug load.
2) Incomplete release.
3) In vivo variability in single unit pulsatile drug delivery system.
4)Immediate withdrawal of drug is not possible.

IV. DIFFERENT MARKETED TECHNOLOGY:

Such as Pulsicap, Diffucap®, three-dimensional printing®, CODAS®, OROS®, IPDAS®, GEOCLOCK®, Ritalina®, Uniphyl®, Opara®, ER, [33,37], Timerx® [38,39,40].

1) Spheroidal Oral Drug Absorption System (SODAS): This technology are used for production of control beads. They control the release of drug during 24 hours. An additional option is pulsatile release, where a once daily dosage form can resemble multiple daily doses by releasing drug in discrete bursts throughout the day [41].

2) Chronotherapeutic Oral Drug Absorption System (CODAS): This technology are advance in release of drug after the prolong period time of drug release. A good example is Verelan® PM, which was designed to release Verapamil approximately four to five hours after ingestion [4]. When drug system passed through GIT they contains layers , water insoluble polymer layer play the main role in drug release from device. When taken at bedtime, this controlled onset extended release delivery system enables a maximum plasma concentration of Verapamil in the morning hours, when blood pressure normally is high [42].

3) GEOCLOCK® Technology : GEOCLOCK Tablet are contain the outer layer made by mixing polymer material have hydrophobic in nature they protect the drug from intestine and stomach PH. SkyePharma has used this novel technology to develop Lodotra™, a rheumatoid arthritis drug, which delivers the active pharmaceutical ingredient at the most suitable time of day to treat the disease condition [43].

4) EURANDs pulsatile and chrono release System: This system capable for provide the various layer to control the release of drugs substance. When administered at bedtime, Propranolol is released after the initial delay such that maximum plasma level occurs in the early morning hours, when the patient is mostly at risk [44].

Technology	Mechanism	Proprietary name and dosage form	API	Disease	Reference
OROS®	Osmotic mechanism	Covera-HS®; XL tablet	Verapamil HCL	Hypertension	45
CODAS®	Multi-particular pH dependent system	Verelan® PM; XL release capsule	Verapamil HCL	Hypertension	46
DIFFUCAPS®	Multi-particulate system	Innopran®; XL tablets	Verapamil HCL, Propranolol HCL	Hypertension	47
Three-dimensional printing®	Externally regulated system	TheirForm™	Diclofenac Sodium	Hypertension	48
Pulsincap™	Rupturable system	Pulsincap™	Dofetilide	Hypertension	49

Table 2- Marketed technologies of pulsatile drug delivery

V. FACTOR AFFECTING RELEASE OF DRUG FROM DEVICE.

1) MOLECULAR WEIGHTS: Mechanical strength of polymer depends on the Molecular weight. Higher Molecular weight they difficult in release of drugs from device.

2) CONCENTRATIONS OF POLYMER: Optimum concentration of polymer produce the maximum effects; varies in concentration they effect the rate of release.

3) FLEXIBILITY OF POLYMER: Greater flexibility cause greater diffusion into membrane, decrease in flexibility of polymer chain difficult in diffusion across the membrane. when the concentration of the polymer is too low as compare to the concentration of liquid medium, the number of polymer chains per unit volume of liquid medium is less, the mucoadhesive strength of polymer at that concentration is also very less.

4) HYDROGEN BONDING CAPACITY: Hydrogen bonds are most affect major factor in drug delivery system they , this bond are create by the COOH, OH group presence.

VI. CONCLUSION:

Using day time, night time necessity, extensive first passed metabolism, absorption of drug in GIT without irritation, colon targeted drug delivery system, PDDS offer the key for delivery of drugs exhibiting chrono-pharmacologicalbehavior, release of drug immediately at the time, PDDS should be promising in the future.

REFERENCES

[1]. Evans RM, Marian C, et al., eds., (1996) " Taking your medication: A question of Timing, Chicago, IL. American medical Association". Page no- 3-8.

[2]. Washington N, Washington C, Wilson C.G, (2001);" chapter 5 the stomach " physiological pharmaceutics: Barriers to drug absorption" 2nd Edition, Taylor & francls, page no- 75-108

[3]. Bussemer T, Otto I, Bodemeier. Pulsatile drug delivery system critRev. there drug Carrier.system2001; 18(5):433-58.

[4]. Sharma GS, Srikanth MV, Uhamwangho, phani kumar KS &Ramana murthy KV.recent treads in pulsatile drug delivery system-A review2(2010)200-212.

[5]. Evans RM, Marian C, et al., eds., (1996) " Taking your medication: A question of Timing, Chicago, IL. American medical Association". Page no- 3-8.

[6]. Washington N, Washington C, Wilson C.G, (2001);" chapter 5 the stomach " physiological pharmaceutics: Barriers to drug absorption" 2nd Edition, Taylor& francls, page no- 75-108.

[7]. Cai K, Luo Z, Hu Y, " Magnetically triggered reversible controlled drug delivery frommicrofabricated polymeric multireservoir devices" , (2009), 21,page no - 4045-4049.

[8]. Kost J and Langer R. advantage drug Del rev 2001, 46:125-148.

[9]. Sangall ME, Maroni A, Foppoli A. European journal of pharmaceutical science2004; 22; 469-476.

[10]. Crison JR,Siersma PR,Amidon GL.A novel programmable oral release technology for delivering drug, human feasibility testing using gamma scintigraphy. Proccer Intern symptoms control rel bioact mater 1996; 23:51-52.

[11]. Linkwitz A, Magruder JA, Merrill S. Osmotically Driven Delivery Device with Expandable Orifice for Pulsatile Delivery Effect. US Patent No. 5,318,558; 1994.

[12]. Linkwitz A, Magruder JA, Merrill S. Osmotically Driven Delivery Device with Expandable Orifice for Pulsatile Del

[13]. Magruder PR, Barclay B, Wong PSL, Tgeeuwes F. Composition comprising salbutamol. US Patent No.4751071:1988.

[14]. Gutowska A, Bark JS, Kwon IC, Bae YH ,Kin SW. Squeezing hydrogen for controlled oral drug delivery .J control Rel1997;48:141-148.

[15]. Yui N, Okano T, Sakurai Y.Inflammation responsive degradation of cross linked hyaluronic acid gels. J control rel 1992; 22:105-116.

[16]. Grover chandani, Bhatt Ganesh, Kothiyal preeti." A comprehensive review of pulsatile drug delivery system (2012), page no- 99.

[17]. Sachin sanvase, Neeraj kumar .pulsatile drug delivery; current scenario. CRIPS 2007; 8:27-33.

[18]. Santini JT, Cima MJ, Langer R.A controlled release microchip. nature 1999;335-338.

[19]. Nitin S, Satarkar, Zach hilt S, Magnetic hydrogel Nanocomposites for remote controlled pulsatile drug release. J cont release 2008; 130:246-251.

[20]. Botti B, Youan C: " chronopharmaceuticals: gimmick or Clinical relevant approach to

drugs delivery, John. Control Rel. (2004); 98(3): page no - 337-353.
[21]. D.K.Singh, A.S.poddar, S.U Nigade, S.S.poddar.pulsatile drug delivery system: An overview 2011.
[22]. Vipul P.Patel, Tushar R. Desai, Chetal R. Matholia, Arjun S. Dedakia. " Pulsatile drug delivery system : A review
[23]. Tiger G.H, Brzezinski D, Schafer A.I., czeisler C.A, Rutherford J.D, Willich S.N., Gleason R.E., Williams G.H, muller J.E.,(1987) " concurrent morning increase in platelet aggregability and the rise of myocardial infraction and sudden cardiac death ". New Emgl.j.Med.316. Page no: - 1514-1518.
[24]. Muller J.E., Tofer G.H., Stone P.H., (1989) "Circadian variation and triggers of onset of acute cardiovascular disease ". Circulation 79, page no.733 - 743.
[25]. Arkinstall W.W. (1988) " Review of the North American experience with evening administration of uniphyl tables, a once - daily theophylin preparation, in the treatment of nocturnal asthma " A.M.J.med. 85, page no. 60-63.
[26]. Kraft M, Martin R.J., (1995) "chronobiology & Chronotherapy in medicine "Dis.Monit. 41 Page no.501 - 575.
[27]. Patel Tejaskumar, Mahantesh Ananthapur, Sabitha J.S, Sourav Tribedi, Rinku Mathappan, Prasanth V.V. " Formulation & evaluation of erodible pulsatile drug delivery system of salbutamol sulphate for nocturnal Asthma" (2013) 3,3.
[28]. Matiholimath VS, Dandagi PM, Jain SS, Gdad AP, Kulkarni AR,"Time and PH dependent colon specific, pulsatile delivery of theophyline for nocturnal asthma",2007,328, pg. no. 49-56.
[29]. Abraham S, Srinath MS, "Development of modified Pulsatile drug delivery system of metronidazole for drug tareting", 2007, 69(1) pg.no: 18-23.
[30]. Tiran J., Galle K.R., Porte Jr D, (1975) "A simulation model of extra cellular glucose distribution in the human body ". Ann.Biomed.Eng, 3, page no- 34-46.
[31]. Auvil- Novak S.E, (1999) "The chronobiology, chronopharmacology, and chrono therapeutics of pain, Amnu.Rev. Nuts.Red.17. Page no- 133-153.
[32]. Sander S.W., Moore J.G., (1992) " Gastrointestinal chronopharmacology: Physiology, pharmacology, and therapeutic implications, pharmacol" 54 page no- 1-15.
[33]. Hrushesky W.J., lannim D., Hays E, (1998) "Evidence for an ontogenetic basis for circadiancoordination of cancer cell proliferation" J. Natl. Chacer Inst.90 page no- 1480-1484.
[34]. Hrushesky W.J., Bjarnason G.A., "Circardian cancer therapy "(1993) J.clin.Oncol 11 page no- 1403-1417.
[35]. Mayer D., (1976) " The circadian rhythm of synthesis & Catabolism of cholesterol: Arch.Toxicol.36 page no- 267-276
[36]. Dalvadi H, Patel JK, chronopharmaceutics, " Pulsatile Drug delivery system as current trend ". 2010,5(5), page no- 204-230.
[37]. Sweta Arora, J.Ali, Alka ahuja. Sanjula baboata and J. Qureshi " pulsatile drug delivery system: An approach for controlled drug delivery " Indian journal of pharmaceutical science.2006,68 (3).
[38]. https://en.wikipedia.org/wiki/Passive_transport.
[39]. Goff W.L., Guerin M., Chapmand. E Bruckert., (2001) circadian & interindividual variations of cholesterol synthesis , sang thromb . Aviss.13 page no- 461-467.
[40]. Gupta Nitan Bbarti, Sharma Pooja, Bhndari Neeraj, Singh kulwinder, Kumari Asha."Pulsatile drug delivery As modified release dosage form: A review" 2012, 2(6), pg.no. 102-110.
[41]. Survase S, Kumar N." Pulsatile drug delivery: current scenario".CRIPS.2007; 8: page no 23-7 [Google scholar].
[42]. Roy P, Shahiwala A, " Multiparticulate formulation approach to pulsatile drug delivery: Current perspective, J.Control Release, (2009), 134, page no- 17-80.
[43]. Dvane, John G, Stark, Paul, Fanning, Niall MM. Multiparticulate modified release composition. US Patent No.4863742 2009.
[44]. White WB, Mehrotra DV, Black HR, Fakouhi TD. Effects of controlled onset extended release Verapamil on nocturnal blood pressure (dippers versus nondipprs)-verapamil study group; Am J Cardiol 1997;80:469-474.
[45]. Gopi Venketesh. New tools for timed, pulsatile drug delivery. Pharma Formu & Qual 2005.
[46]. Parcel P, Vishnupad KS, Venkatesh GM. Timed pulsatile drug delivery systems. US Patent 6,627,2231.

[47]. Jao F, Wong P, Huynh H, et al. (1992):17
[48]. Panoz D and Geoghegan E (1989):49
[49]. Percel P, Vishnupad K and Venkatesh G (2002):13
[50]. Katstra WE, Palazzolo RD, Rowe CW, et al. (2000) J. Control. Rel. 66:1-9
[51]. Stevens HNE, Wilson CG, Welling PG, et al. (2002) Int. J. pharm. 236:27-34