

Review Article

Pulsatile Drug Delivery System: An OverviewREWARS^{*1}, BANSAL BK¹, SINGH CJ², SHARMA AK¹, PAREEK R¹¹Department of pharmaceuticals, Arya College of pharmacy, Jaipur – 302028, Rajasthan²Department of pharmacology, Arya College of pharmacy, Jaipur – 302028, Rajasthan**ARTICLE DETAILS***Article history:*

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ABSTRACT

Pulsatile drug delivery systems (PDDS) are gaining importance as these systems deliver the drug at specific time as per the pathophysiological need of the disease, resulting in improved patient therapeutic efficacy and compliance. A Pulsatile drug release, where the drug is released rapidly after a well-defined lag-time, could be advantageous for many drugs or therapies. A pulse has to be designed in such a way that a complete and rapid drug release is achieved after the lag time so as to 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. Various techniques are available for the pulsatile delivery like pH dependent systems, time dependent systems, etc. Pulsatile release systems can be classified in multiple-pulse and single-pulse systems. A popular class of single-pulse systems is that of rupturable dosage forms. Advantages of the Pulsatile drug delivery system are reduced dose frequency; reduce side effects, drug targeting to specific site like colon and many more. Now in market various technologies of pulsatile drug delivery system like Pulsincap, Diffucaps etc. are launched by pharmaceutical companies.

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INTRODUCTION

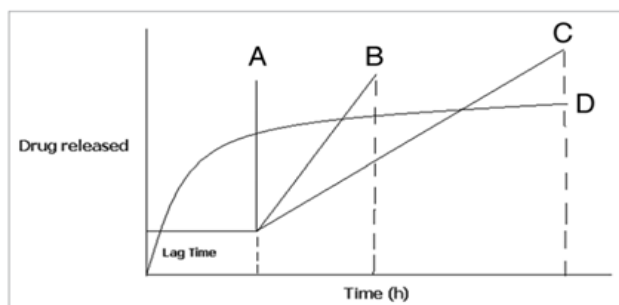
The newer technologies are developing in pharmaceutical field. The most efficacious dosage forms are generated on already existing molecules because many hurdles occur during discovery of the new molecules [1]. Pulsatile drug delivery system is gaining a lot of interest and attention now a day. Though most delivery system is designed for constant drug release over a prolonged period of time, PDDS are characterized by a programmed drug release, as constant blood level may not always be desirable. These systems have a typical mechanism of delivering the drug rapidly and completely after a lag time [2]. In traditional days, drug delivery has meant for getting a simple chemical absorbed predictably from the gut or from the site of injection. A second generation drug delivery goal has been the perfection of continuous, constant rate delivery of bioactive agents. However, living organisms are not "zero-order" in their requirement or response to drugs.

They are predictable resonating dynamic systems, which require different amounts of drug at predictably different times within the circadian cycle which will maximize desired and minimize undesired drug effects [3].

Modified release dosage forms have a great importance in this regard. Such systems control the release pattern of drug, either with constant or variable rates drug is released with predetermined release rates. However, there are certain conditions for which such a release pattern is not suitable. These conditions demand release of drug after a lag time. This condition can be achieved by Pulsatile drug delivery system which is defined as the rapid and transient release of certain amount of molecules within a short time period immediately after a predetermined off- release period i.e. lag time. A pulse has to be generated in such a way that a complete and rapid drug release is achieved after the lag time so as to match body's circadian rhythms with the release of drugs [4].

***Author for Correspondence:**

Email: Ph.12sr@gmail.com



Where (A) sigmoidal release after lag time (B) delayed release after lag time (C) sustained release after lag time (D) extended release without lag time.

Figure 1: Shows Schematic representation of different drug delivery systems

In this graph, it was aimed to achieve a sigmoid release pattern (Fig. 1). The characteristic feature of the formulation was a well-defined lag time followed by a drug pulse with the enclosed active quantity being released at once. Thus, the major challenge in the development of pulsatile drug delivery system is to achieve a rapid drug release after the lag time. Often, the drug is released over an extended period of time (patterns b & c in Fig. 1).

A new concept of chronopharmaceutics has emerged, wherein research is devoted to the design and evaluate the drug delivery systems that release a therapeutic agent at a rhythm that ideally matches the biological requirement of a given disease therapy^[5].

Chronopharmacotherapy: Recent studies show that diseased have predictable cyclic rhythms and the timing of medication regimens can improve outcome in selected chronic conditions.

The “Chronopharmaceutics” consist of two words chronobiology and pharmaceutics. Chronobiology is the study of biological rhythms and their mechanisms^[6]. There are three types of mechanical rhythms in our body, they are: Circadian, Ultradian and Infradian.

1. **Infradian Rhythms:** Oscillations that are longer than 24 hours are termed as Infradian Rhythms (less than one cycle per 24hours) e.g. Monthly Menstruation^[7].
2. **Ultradian Rhythms:** Oscillations of shorter duration are termed Ultradian Rhythms (more than one cycle per 24 h). E.g. 90 minutes sleep cycle^[7].
3. **Circadian Rhythms:** Circadian rhythms are self-sustaining, endogenous oscillations that occur with a periodicity of about 24 Hours

(Fig. 2). These rhythms allow organism to anticipate and prepare for precise and regular environment changes. There are clear patterns of core body temperature, brain wave activity, hormone production, and other biological activities linked to this cycle. Some people function best in the morning while others have their peak in the noon or evening. If our normal rhythm is disrupted we tend to become anxious e.g. many people have difficulty in adjusting to swing-shift work schedules. In sleep wake cycle, an animal will settle into a 24 hour cycle activity and sleep even if deprived of light. Diurnal blood pressure fluctuations are super imposed by a 24-hour rhythm with lower levels during the night and higher in the day^[9, 10].

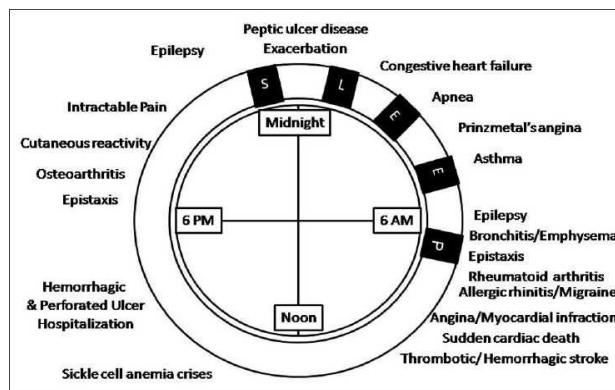


Figure 2: Cycle of circadian rhythm

Chronotherapy: Co-ordination of biological rhythms and medical treatment is called chronotherapy^[8].

Chronotherapeutics: Chronotherapeutics is the discipline concerned with the delivery of drugs over a certain period of time^[11]. Pattern of drug release in which the drug concentration is maintained in the therapeutic window for a prolonged period of time, thereby ensuring sustained therapeutic action. However, there are certain conditions for which such a release pattern is not suitable. These conditions demand release of drug after a lag time. Such a release pattern is known as Pulsatile release. Recent studies have revealed that diseases have a predictable cyclic rhythm and that the timing of medication regimens can improve the outcome of a desired effect^[12].

Table 1: Diseases which follows Chronological behavior

Chronological behavior	Drugs used	Diseases
Acid secretion is high in the afternoon and at night	H2 blockers	Peptic ulcer
Precipitation of attacks during night or at early morning	β 2 agonist, Antihistamines	Asthma
BP is at its lowest during the sleep cycle and rises steeply during the early morning	Nitroglycerin, calcium channel blocker, ACE inhibitors	Cardiovascular diseases
Pain in the morning and more pain at night	NSAIDs, Glucocorticoids	Arthritis
Increase in blood sugar level after meal	Sulfonylureas Insulin, pioglitazone	Diabetes mellitus
Cholesterol synthesis is generally higher during night than day time	HMG CoA reductase inhibitors Hypercholesterolemia	Hypercholesterolemia

Advantages of PDDS: [13][14]

- Extended day time or night time activity.
- Reduced side effects.
- Reduced dose size and dosing frequency.
- Improved patient compliance.
- Daily fewer dosage units are required by patients in the therapy and hence daily cost is lowered.
- Drug adapts to suit circadian rhythms of body functions or diseases.
- Drug targeting to specific site like colon.
- Protection of mucosa from irritating drugs.
- Drug loss is prevented by extensive first pass metabolism e.g. proteins and peptide.
- Avoid biological tolerance (e.g. Tran dermal nitroglycerine).

Disadvantages of PDDS: [15][16]

- Low drug loading capacity and incomplete release of drug.
- Higher cost of production.
- Large number of process variables.
- Lack of manufacturing reproducibility and efficacy.
- Batch manufacturing process.
- Unpredictable IVIVC.
- Need of advanced technology.

Need of PDDS:

- Their activity increases or decreases with time. A number of hormones like rennin, aldosteron, and cortisol show daily as well as timely fluctuations in their blood levels. Circadian effects are also observed in case of pH and acid secretion in stomach, gastric emptying, and gastro-intestinal blood transfusion.

- Acid secretion, gastric emptying, cholesterol synthesis, and gastrointestinal blood transfusion may alter with circadian rhythm.
- Chronopharmacotherapy of diseases which shows circadian rhythms in their path physiology like bronchial asthma, myocardial infarction, angina pectoris, rheumatic disease, ulcer, and hypertension.
- Lag time is essential for those drugs undergo acidic degradation (e.g. peptide drugs) that irritate the gastric mucosa or induce nausea and vomiting.
- Targeting a drug to distal organs of gastrointestinal tract (GIT) like the colon the drug release should be prevented in the upper two-third portion of the GIT.
- Drugs undergoes extensive first pass metabolism that easily given by Pulsatile drug delivery system.
- Drugs that produce biological tolerance due to continuous exposure of drug in body. This system tolerance by giving lag time [19][20].

Diseases Requiring Pulsatile Delivery: Recent studies have revealed that diseases have predictable cyclic rhythms and that the timing of medication regimens can improve outcome in selected chronic conditions [17][18]. The list of diseases which are required pulsatile release given in Table 1.

Mechanism of drug release from pulsatile drug delivery system:

The mechanism of drug release from PDDS can be occurring in the following ways [21].

Diffusion: Water diffuses into the interior of the particle when particle come in contact with aqueous fluids in the gastrointestinal tract and resultant drug solutions diffuse across the release coat to the exterior.

Erosion: Some coatings designed to erode gradually with time, result in the release of drug contained within the particle.

Osmosis: An osmotic pressure can be built up within the interior of the particle when water allows entering under the right circumstances. The drug is forced out of the particle into the exterior through the coating.

METHODS OF DEVELOPMENT OF PULSATILE DRUG DELIVERY SYSTEM: Methodologies for the PDDS can be broadly classified into four classes [22];

- I. Time controlled Pulsatile release
 - A. Single unit system
 - B. Multi-particulate system
- II. Stimuli induced
 - A. Thermo-Responsive Pulsatile release
 - B. Chemical stimuli induced Pulsatile systems
- III. External stimuli Pulsatile release
 - A. Electro responsive Pulsatile release
 - B. Magnetically induced Pulsatile release
- IV. Pulsatile release systems for vaccine and hormone products

I. TIME CONTROLLED PULSATILE RELEASE SYSTEM:

These time-controlled systems can be classified as single unit (e.g., tablet or capsule) or multiple unit systems.

A. Single Unit Systems:

Single-unit systems are mostly developed in capsule form. The lag time is controlled by a plug, which gets pushed away by swelling or erosion, and the drug is released as a "Pulse" from the insoluble capsule body.

1. Capsular system: Single-unit systems are mostly developed in capsule form. The lag time is controlled by a plug, which gets pushed away by swelling or erosion, and the drug is released as a "Pulse" from the insoluble capsule body. Pulsincap® was developed by R. P. Scherer International Corporation, Michigan, US, and is one such system that comprises 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 this capsule came in contact with the dissolution fluid, it swelled; and after a lag time, the plug

pushed itself outside the capsule and rapidly released the drug. Polymers used for designing of the hydro gel plug were various viscosity grades of hydroxyl propyl methyl cellulose, poly methyl methacrylate, poly vinyl acetate and poly ethylene oxide. The length of the plug and its point of insertion into the capsule controlled the lag time. Pulsincap® was studied in human volunteers and was reported to be well tolerated. A low-volume diagnostic test kit was marketed in 1997 under the trade name of 'Sprin salmonella' by Oxoid Ltd., Basingstoke, U.K. developed Pulsincap® system with erodible compressed tablet[23][24][25].

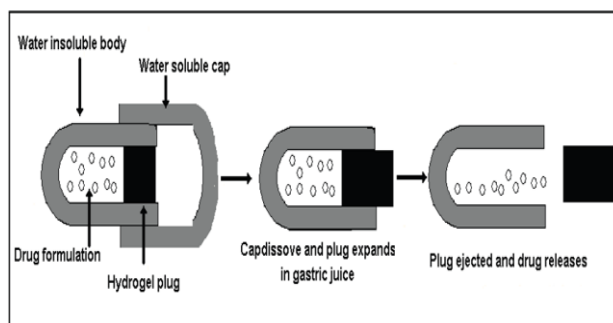


Figure 3: Schematic diagram capsular system

2. Osmosis based system: This system contains a drug and a water-absorptive osmotic agent that is placed in compartments separated by a movable partition. The Pulsatile delivery is achieved by a series of stops along the inner wall of the capsule. These stops obstruct the movement of the partition but are overcome in succession as the osmotic pressure rises above a threshold level. This system was used to deliver porcine somatotropin. Osmotic delivery capsules ("osmotic pumps") function by virtue of walls which selectively pass water into the capsule reservoir. Absorption of water by the capsule through these walls is driven by a water-attracting agent in the capsule interior which creates osmotic pressure across the capsule wall. The water-attracting agent may be the beneficial agent itself whose controlled release is sought, but in most cases, it is a separate agent specifically selected for its ability to draw water, and this separate agent is being isolated from the beneficial agent at one end of the capsule.

In either case, the structure of the capsule wall does not permit the capsule to expand, and as a result, the water uptake causes discharge of the beneficial agent through an orifice in the capsule at the same rate that water enters by osmosis.

Examining the patent literature of Pulsatile osmotic pumps several systems were described during time. In one case, the Pulsatile effect of a drug is achieved by combining the drug with a modulating agent. The modulating agent is selected on the basis of its solubility in the delivery medium relative to the beneficial agent and the Pulsatile effect results from one of the two agents falling below its saturation point, causing more of the other to go into solution and to thereby be released^{[26][27]}.

a) Port® System: The Port® System consists of a gelatin capsule coated with a semi permeable membrane (e.g., cellulose acetate). Inside the capsule were an insoluble plug and an osmotically active agent along with the drug formulation. When this capsule came in contact with the dissolution medium, water diffuses across the semi permeable membrane, resulting in increased pressure inside that ejects the plug after a predetermined lag time. The lag time is controlled by coating thickness^[28]

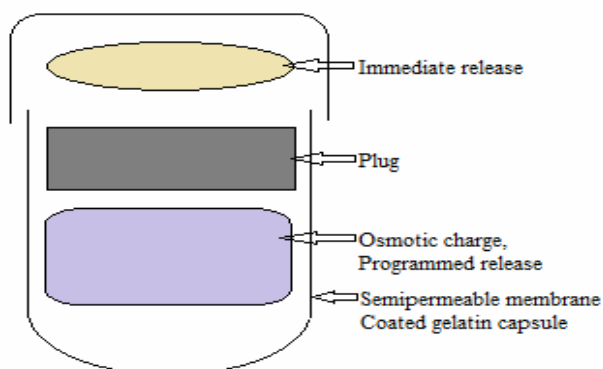


Figure 4: Port System

b) Delivery system with soluble or erodible membranes: In such systems the drug release is controlled by the dissolution or erosion of the outer coat which is applied on the core containing drug. Time dependent release of the active ingredient can be obtained by optimizing the thickness of the outer coat. E.g. chronotropic system which consists of a drug containing core layered with HPMC optionally coated with an outer enteric coating.

The lag time prior to drug release is controlled by the thickness and the viscosity grade of HPMC layer. Solid dosage form coated with lipid barriers such as carnauba wax & beeswax along with surfactants like polyoxyethylene sorbitan monooleate. When this system comes in contact with the aqueous medium the coat emulsifies or

erodes after the lag-time depending on the thickness of coat^[29].

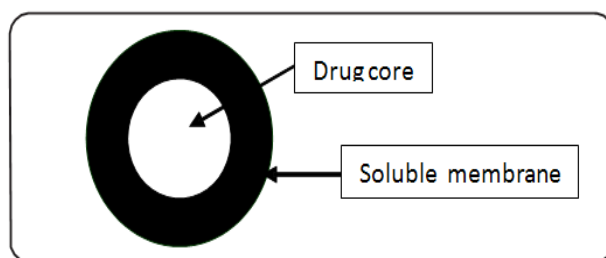


Figure 5: Delivery System with Soluble or Erodible Membranes

c) Delivery System With Repturable Coating: These systems are based up on a reservoir system coated with a rupturable membrane. The outer membrane ruptures due to the pressure developed by effervescent agents (or) swelling agent. Citric acid & sodium bicarbonate is incorporated as effervescent mixture in tablet core coated with ethyl cellulose, when system comes in contact with water it produces carbon dioxide gas which exerts pressure & after lag time rupture the membrane & rapid release of drug occurs. A reservoir system with a semi permeable coating is proposed especially with drugs with high first pass effect in order to obtain in-vivo drug pattern similar to the administration of several immediate release doses croscarmellose sodium starch.

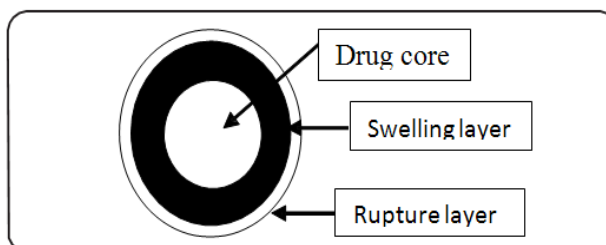


Figure 6: Delivery System with Repturable Coating.

Glycollate or low substituted hydroxy propyl cellulose were used as swelling substances, which resulted in complete film rupture followed by rapid drug release. The lag time is controlled by composition of outer polymeric membrane^{[30][31]}. Sungthongjeen et al developed a tablet system consisting 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^[32].

B. Multi-particulate system: Systems Based on Change in Membrane Permeability:

Numerous pharmaceutical forms with delayed release for oral administration are available. As already mentioned the release of the drug must be controlled according to therapeutically purpose and the pharmacological properties of the active ingredient. In consequence, it is not always desirable the blood levels to be constant. On the contrary, in order to avoid any habituation and in order to limit the side effects provoked by the active ingredient, it would be absolutely advantageous for the plasmatic rate to follow the metabolic rhythm and the specific needs of the patient during certain periods. For instance, in order to diminish the nocturnal symptoms or the symptoms upon awakening in the case of certain chronic diseases such as ischemic heart disease, asthma and arthritis, the drugs should be administered in such a way that the desired therapeutical plasmatic level is reached only at the desired moment, i.e. during sleep or at the moment of awakening.

Chen described a system composed of a large number of pellets made up of two or more populations of pellets or particles. Each pellet contains a drug containing core, and a water soluble osmotic agent enclosed in a water permeable, water-insoluble polymer film. Incorporated into the polymer film is a hydrophobic, water insoluble agent which alters the permeability of the polymer film. The film coating of each population of pellets differs from the coating of every other population of pellets in the dosage form in the rate at which water passes through to the core and the rate at which drug diffuses out of the core. The osmotic agent dissolves in the water, causing the pellet to swell and regulating the rate of diffusion of drug into the environment of use. As each population of pellets releases drug into the environment sequentially, a series of Pulsatile administrations of the drug from a single dosage form is achieved [33].

II. CLASSIFICATION OF PDDS BASED ON STIMULI INDUCED:

A. TEMPERATURE INDUCED SYSTEM: (Thermo-Responsive Pulsatile release) Thermo-responsive hydrogel systems have been developed for Pulsatile release. In these systems the polymer undergoes swelling or deswelling phase in response to the temperature which

modulate drug release in swollen state. Y.H. Bae et al developed indomethacin Pulsatile release pattern in the temperature ranges between 20°C and 30°C by using reversible swelling properties of copolymers of N-isopropylacrylamide and butyrylacrylamide. Kataoka et al developed the thermo sensitive polymeric micelles as drug carrier to treat the cancer. They used endfunctionalized poly (N isopropylacrylamide) (PIPAAm) to prepare corona of the micelle which showed hydration and dehydration behavior with changing temperature [34][35].

B. CHEMICALLY INDUCED SYSTEM:

There has been much interest in the development of stimuli-sensitive delivery systems that release a therapeutic agent in presence of specific chemical moieties like enzyme or protein. One of the good examples is Glucose-responsive insulin release devices in which insulin is release on increasing of blood glucose Level. In diabetes mellitus there is rhythmic increase in the levels of glucose in the body requiring injection of the insulin at proper time. Several systems have been developed which are able to respond to changes in glucose concentration. One such system includes pH sensitive hydrogel containing glucose oxidase immobilized in the hydrogel. When glucose concentration in the blood increases glucose oxidase converts glucose into gluconic acid which changes the pH of the system. This pH change induces swelling of the polymer which results in insulin release. Insulin by virtue of its action reduces blood glucose level and consequently gluconic acid level also gets decreased and system turns to the deswelling mode thereby decreasing the insulin release [36].

Yui et al. designed drug delivery systems based on the polymers which responded to the hydroxyl radicals and degraded in a limited manner. Yui and co-workers used hyaluronic acid (HA), in the body, HA is mainly degraded either by hydroxyl radicals or a specific enzyme, hyaluronidase. Degradation through hydroxyl radicals however, is usually dominant and rapid when HA is injected at inflammatory sites. Thus, they designed crosslinked HA with ethylene glycol diglycidylether or polyglycerol polyglycidylether. Thus, a surface erosion type of degradation was achieved. Patients with inflammatory diseases, such as rheumatoid arthritis, can be treated using this type of system [37][38].

In Enzymatically- Activated liposomes, drug loaded liposomes was incorporated into microcapsules of alginate hydrogels. Liposomes

inside the microcapsules were coated with phospholipase A2 to achieve a Pulsatile release of drug molecules. Phospholipase A2 was shown to accumulate at the water/liposome interfaces and remove an acyl group from the phospholipids in the liposome. Destabilized liposomes release their drug molecules, thus allowing drug release to be regulated by the rate determining microcapsule membrane [39].

Miyata et al. focused on the development of stimuli responsive crosslinking structures into hydrogels. Special care was given to antigen-antibody complex formation as the cross-linking units in the gel, since specific antigen recognition of an antibody can provide the foundation for a new device fabrication. Using the difference in association constants between polymerized antibodies and naturally derived antibodies towards specific antigens, reversible gel swelling/deswelling and drug permeation changes could occur. Thus, biological stimuli responsive hydrogel were created [40].

III. External stimuli Pulsatile release: For releasing the drug in a Pulsatile manner, another way can be the externally regulated systems in which drug release is programmed by external stimuli like magnetism, ultrasound, electrical effect and irradiation.

A. ELECTRICALLY STIMULATED: Electrically responsive delivery systems are prepared by poly electrolytes (polymers which contain relatively high concentration of ionisable groups along the backbone chain) and are thus, pH-responsive as well as electro-responsive. Under the influence of electric field, electro responsive hydrogels generally bend, 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 electroresponsive drug delivery system was developed by R. V. Kulkarni, et al., using poly (acrylamide-grafted-xanthan gum) (PAAm-g- XG) hydrogel for transdermal delivery of ketoprofen [41].

B. MAGNETICALLY STIMULATED: Magnetically regulated system contains magnetic beads in the implant. On application of the magnetic field, drug release occurs because of magnetic beads [42]. Magnetic carriers receive their magnetic response to a magnetic field from incorporated materials in beads such as magnetite, iron, nickel, cobalt etc. Tingyu Liu, et al developed the magnetic hydrogels which was successfully

fabricated by chemically crosslinking of gelatin hydrogels and Fe₃O₄ nanoparticles (ca. 40–60 nm) through genipin (GP) as cross-linking agent. Saslawski et al. [35] developed different formulations for in vitro magnetically triggered delivery of insulin based on alginate spheres. In an experiment, ferrite microparticles (1µm) and insulin powder were dispersed in sodium alginate aqueous solution. The ferrite-insulin alginate suspension was later dropped in aqueous calcium chloride solution which causes the formation of cross linked alginate spheres, which were further cross linked with aqueous solution of poly(L-lysine) or poly(ethylene imine). They described that the magnetic held characteristics due to the ferrite microparticles and the mechanical properties of the polymer matrices could play role in controlling the release rates of insulin from the system [43].

IV. PULSATILE RELEASE SYSTEMS FOR VACCINE AND HORMONE PRODUCTS:

Vaccines are traditionally administered as an initial shot of an antigen followed by repeated booster shots to produce protective immunity [44]. The frequency of the booster shots, and hence the exact immunization- schedule is antigen dependent. Also, co-administration of vaccine adjuvant is often required to enhance the immune response to achieve protective immunity [45]. PDDS offer the possibility of single-shot vaccines if initial booster release of the antigen can be achieved from one system in which timing of booster release is controlled. Vizcarra et al. found in nutritionally anoestrous cows, GnRH administered in pulses of 2 mg over 5 min every hour for 13 days produced a higher frequency of luteal activity by 13th day than cows given continuous infusions or pulses every 4 hr.

Marketed Technologies of Pulsatile Drug Delivery:

Currently pharmaceutical company focused on developing and commercializing Pulsatile drug products that fulfil unmet medical needs in the treatment of various diseases. For several diseases (e.g. bronchial asthma, hypertension, rheumatic disease and myocardial infarction) as well for control of body functions (blood pressure, levels of many hormones e.g. aldosterone, rennin, and cortisol) influenced by circadian rhythms, delayed or Pulsatile drug release could be an optimal approach. Recently develop various technologies that presents in this review are:

1. Pulsincap™ technology: Pulsincap was developed by R.R. Scherer International Corporation (Michigan). This device consists of a non-disintegrating half capsule body sealed at the open end with a hydrogel plug that is covered by a watersoluble cap. The whole unit is coated with an enteric polymer to avoid the problem of variable gastric emptying. When this capsule comes in contact with the dissolution fluid, it swells, and after a lag time, the plug pushes itself outside the capsule and rapidly releases the drug [49]. Another formulation approach was in the form of a bead or granule with a four-layered spherical structure, which consists of a core, a drug, swelling agent (e.g., sodium starch glycolate or carboxy methyl cellulose sodium) and an outer membrane water-insoluble polymer (e.g., ethyl cellulose, Eudragit® RL). The penetration of GI fluids through the outer membrane causes the expansion of the swelling agent. The resulting stress due to swelling force leads to the destruction of the membrane and subsequent rapid drug release. Polymers used for designing the hydrogel plug were various viscosity grades of hydroxyl propyl methyl cellulose, polymethylmethacrylates, polyvinyl acetate and poly ethylene oxide. Another new approach was enteric-coated, timed-release, press-coated tablets (ETP tablets). These tablets were developed by coating enteric polymer on timed-released, press-coated tablets composed of an outer shell of hydroxyl propyl cellulose and core tablets containing diltiazem hydrochloride as a model drug [46][47]. Patel and Patel developed a modified Pulsincap device containing diclofenac sodium to target the drug in the colon. This is a site-specific and time-dependent formulation; i.e., by administering the formulation at bed time, symptoms that are experienced early in the morning are avoided. This therapeutic effect is prolonged by continuously releasing the medication over an extended period of time after administering a single dose. The objective of the study was to explore the time and pH-dependent controlled drug delivery of Diclofenac Sodium using the pulsincap system [48].

2. Orbexa® Technology: Developed by Aptalis Pharmaceutical Technologies. Orbexa technology is a multiparticulate system that enables high drug loading and is suitable for products that require granulation. This technology consists of beads of a controlled size and density using granulation/extrusion and spheronization techniques. These beads provide higher drug

concentration, can be coated with functional polymer membranes for additional release rate control and can also be used for sensitive drugs such as proteins, enzymes. This technology can be used for gastric protection, delayed release, sustained release, site-specific delivery, Pulsatile delivery, complex release pattern, separation of incompatibles and combination products. Orbexa beads can be filled into capsules or single-dose sachet [50].

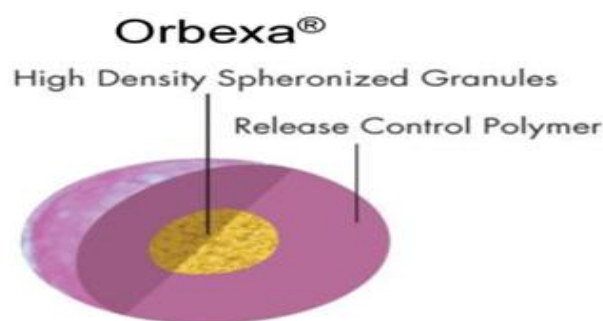


Figure 7: ORBEXA® Technology

3. DIFFUCAPS® Technology: Diffucaps is a multiparticulate bead system comprised of multiple layers of drug, excipients, and release-controlling polymers are shown in Fig. The beads contain a layer of organic acid or alkaline buffer to control the solubility of a drug by creating an optimal pH microenvironment for drugs that exhibit poor solubility in intestinal pH, in environments with pH greater than 8.0. Alternatively, the beads can contain a solid solution of drug and crystallization inhibitor to enhance bioavailability by maintaining the drug in its amorphous state. Diffucaps technology is especially suitable for drugs that traditionally require multiple daily doses or drugs needing customized release formulations [51].

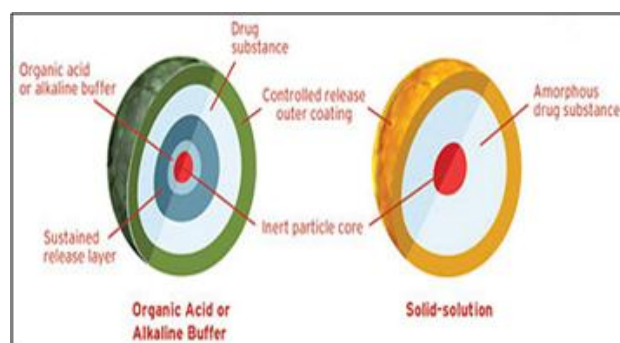


Figure 8: DIFFUCAPS® technology

4. DIFFUTAB® Technology: Diffutab technology enables customized release profiles and region-specific delivery. Diffutab® technology uses a blend of hydrophilic and hydrophobic polymers to control drug release via diffusion through, and

erosion of, a matrix tablet. Diffutab is particularly useful for high-dose products and drugs that require sustained release and/or once-a-day dosing [52][53].

Advantages of Diffutab

- Matrix tablet utilizes a combination of water soluble particles and active drug
- Suitable for high drug loading
- Supports sustained-release, once-a-day dosing.

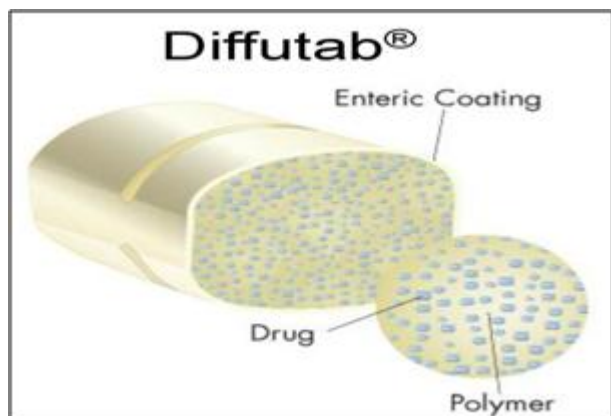


Figure 9: Diffutab® technology

5. SODAS® Technology: (Spheroidal Oral Drug Absorption System) This technology is based on the production of controlled release beads and it is characterized by its inherent flexibility, enabling the production of customized dosage forms that respond directly to individual drug candidate needs. SODAS can provide a number of tailored drug release profiles, including immediate release of drug followed by sustained release to give rise to a fast onset of action, which is maintained for 24 hours. However, the opposite scenario can be achieved where drug release is delayed for a number of 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 [54].

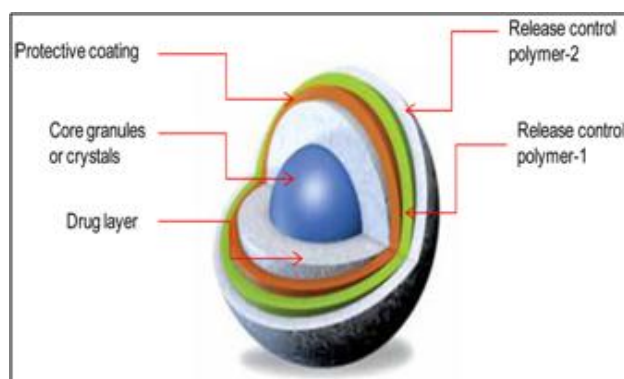


Figure 10: SODAS® Technology

6. PRODAS® Technology: Programmable Oral Drug Absorption System (PRODAS® Technology) is a multiparticulate technology, which is unique in that it combines the benefits of tableting technology within a capsule. The PRODAS® delivery system is presented as a number of minitabets combined in a hard gelatine capsule. Very flexible, the PRODAS® technology can be used to pre-program the release rate of a drug. It is possible to incorporate many different minitabets, each one formulated individually and programmed to release drug at different sites within the gastro-intestinal tract. It is also possible to incorporate minitabets of different sizes so that high drug loading is possible. PRODAS® technology, by incorporating minitabets with different release rates, can display the characteristics of a number of different conventional dosage forms:



Figure 11: PRODAS® Technology

7. CONTIN® Technology: Developed by Purdue Pharma. This technology provides for closer control over the amount of drug released to the bloodstream, and benefits patients in terms of reducing the number of doses they need to take every day, providing more effective control of their disease (particularly at night), and reducing unwanted side effect. Molecular coordination complexes are formed between a cellulose polymer and a non-polar solid aliphatic alcohol optionally substituted with an aliphatic group by solvating the polymer with a volatile polar solvent and react the solvated cellulose polymer directly with the aliphatic alcohol, preferably as a melt. This constitutes the complex having utility as a matrix in controlled release formulations since it has a uniform porosity (semi permeable matrixes) that may be varied. This technology has leads to the development of tablet forms for aminophylline, theophylline, morphine, and other drugs [55].

After addition it forms the coordination complex having utility as a matrix in controlled release formulations since it has a uniform porosity which may be varied. It is also applicable for designing of controlled release tablets. This

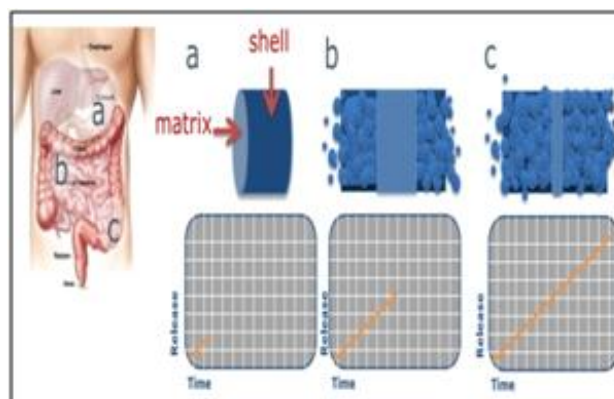
technology has sufficient. It is also applicable for designing of controlled release tablets. This technology has sufficient control over drug release to the blood and reduces the chances of unwanted side effects [56][57].

8. Codas® (chronotherapeutic oral drug absorption system): Elan Corporation, USA, developed CODAS® technology. Delay is introduced by the level of non-enteric release-controlling polymer applied to drug loaded beads. The release-controlling polymer is a combination of water soluble and water insoluble polymers. As water from the gastrointestinal tract comes into contact with the polymer-coated beads, the water soluble polymer slowly dissolves, and the drug diffuses through the resulting pores in the coating. The water insoluble polymer continues to act as a barrier, maintaining the controlled release of the drug [59].

ELANDRUG TECHNOLOGY DEVELOPED CODAS® technology to achieve this prolonged interval. Advantages of the CODAS® technology include a delivery profile designed to complement circadian pattern, controlled onset, an extended release delivery system, rate of release essentially independent of pH, posture and food, "sprinkle" dosing by opening the capsule and sprinkling the contents on food, reduction in effective daily dose and drug exposure, gastrointestinal tract targeting for local effect and reduced systemic exposure to achieve a target profile. Verelan® PM uses the CODAS™ technology, which is designed for bedtime dosing, incorporating a 4 to 5 h delay in drug delivery results in a maximum plasma concentration of verapamil in the morning hours [58].

9. Egalet® Technology: Developed by Egalet Ltd, Denmark. System consists of an impermeable shell with two lag plugs; active drug is sandwiched between the plugs. After the inert plugs have eroded, the drug is released, thus a lag time occurs. Time of release can be modulated by the length and composition of the plugs. This system shows erosion control drug release. The shells are made of slowly biodegradable polymers (such as ethylcellulose) and include plasticizers (such as cetostearyl alcohol), while the matrix of the plugs is made up of a mixture of pharmaceutical excipients including polymers like polyethylene oxide

(PEO). Several opioid products are developed using this technology [60].



(a) Egalet tablet begins, (b) Egalet tablet during release, (c) Egalet tablet has released almost completely

Figure 12: Egalet® Two-Part Oral System

10. IPDAS® (Intestinal protective drug absorption system): A new oral drug delivery approach that is applicable to gastrointestinal (GI) irritant drugs, including the non-steroidal anti-inflammatory drug (NSAID) class. The IPDAS technology is composed of numerous high-density, controlled release beads, which are compressed into a tablet form. Once an IPDAS tablet is ingested, it disintegrates and disperses beads containing a drug in the stomach, which subsequently passes into the duodenum and along the gastrointestinal tract in a controlled and gradual manner, independent of the feeding state. Release of active ingredient is controlled by the polymer system used to coat the beads and/or the micromatrix of polymer/active ingredient formed in the extruded/spheronised multiparticulates. The intestinal protection by this technology is due to the multiparticulate nature of the formulation, which ensures wide dispersion of irritant drug throughout the gastrointestinal tract [61]. The intestinal protection of IPDAS® technology is inherent by virtue of the multiparticulate nature of the formulation, which ensures wide dispersion of irritant drug throughout the gastrointestinal tract. IPDAS® was initially designed as part of the development process for Elan Drug Technologies' proprietary naproxen formulation, Naprelan® [59]. The many advantages of the IPDAS® technology include High density multiparticulate formulation, gastrointestinal protection for more locally irritant drugs (e.g.NSAIDs), advantages of multiparticulate in a tablet form and fast onset if required [62][63].

11. GEOCLOCK® Technology: Developed by SkyePharma. It is in form of chronotherapy focused press-coated tablets. Geoclock® tablets have an active drug inside an outer tablet layer consisting of a mixture of hydrophobic wax and brittle material in order to obtain a pH-independent lag time prior to core drug delivery at a predetermined release rate E.g. LODOTRA – used in rheumatoid arthritis [64]. This dry coating approach is designed to allow the timed release of both slow release and fast release active cores by releasing the inner tablet first after which the surrounding outer shell gradually disintegrates [65]. Skye Pharma 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 [66].

12. Geomatrix® Technology: Developed by Skye Pharma Plc., USA. It is multilayered tablet which consists of a hydrophilic matrix core, containing the active ingredient and one or two impermeable or semi-permeable polymeric coatings (films or compressed barriers) applied on one or both bases of the core which act as surface controlling barriers.

Advantages of the Geomatrix technology are: can achieve simultaneous release of two different drugs and different rates from a single tablet, their ability to be easily incorporated into the production line, can be manufactured by readily available equipment, reproducibility, controlled release of poorly soluble drugs, timed release of drugs, pulsed release of drugs and safety of use. Some of the drugs that are marketed based on this technology are Diltiazem hydrochloride, Nifedipine, and Diclofenac sodium [67][68][69].



Figure 13: Geomatrix TM

13. Pulsys™: Developed by Middle Brook Pharmaceuticals, this enables Pulsatile delivery or delivery in rapid bursts of certain drugs and provides the prolonged release and absorption of a drug [71]. This technology was used to develop chronotherapeutic system for amoxicillin. The

rationale for designing this system was that antibiotics are more effective against fast growing bacteria. On administering immediate release system, bacteria respond to it by going into dormant stage, while Pulsatile system is more effective because pulses of drug release after a regular time interval do not allow bacteria to go into dormant stage. Preclinical studies have shown that approach of using Pulsatile systems is more effective [70].

PULSYS Technology's Moxatag tablet contain Amoxicillin is designed to deliver amoxicillin at lower dose over a short duration therapy in once daily formulation. Advances have also demonstrated that by preclinical studies which improved bactericidal effect for amoxicillin when deliver in Pulsatile manner as compared to standard dosing regimen even against resistant bacteria [72][73].

Minitabs®: Eurand's Minitabs is tiny (2 mm x 2 mm) cylindrical tablets coated with a functional membrane to control the rate of drug release. Eurand Minitabs contain gel-forming excipients that control drug release rate. Additional membranes may be added to further control release rate. The tablets are filled into capsules, allowing a combination of multiple drugs and/or multiple release profiles in the same dosage form. The Eurand Minitabs can be formulated as matrix tablets prior to further coating. Eurand Minitabs can also be used as a sprinkle on food. Eurand Minitabs combine the simplicity of tablet formulation with the sophistication of multiparticulate systems, suitable for high drug loading, and can be used as a sprinkle for pediatric and geriatric patients who have difficulty swallowing tablets [74][75].



Figure 14: Eurand minitabs® technology

15. ACCU-T CR Tri Layer Tablets: ACCU-T CR (controlled release) Tri-Layer Tablets configuration applies controlled release technology to further enhance treatment options.

The ACCU-T CR tablet contains controlled release medication at either end of the tablet separated by a drug free break layer, allowing the CR dose to be divided into exact half doses without affecting the rate of drug release. The majority of conventional CR tablets are not suited for subdividing due to the increase of surface area and the subsequent change in release kinetics. ACCU-T technology provides a solution to this problem and introduces dose flexibility into CR dosage forms. Additionally, an IR (immediate release) component can be added to CR tablets to add even more treatment options and potential product capabilities [76].

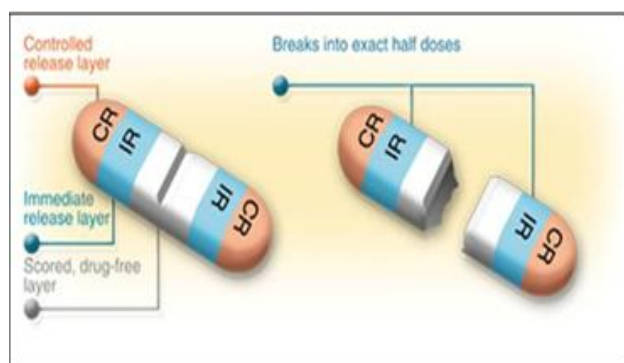


Figure 15: ACCU-T CR Tri-Layer Tablets

16. Banner's Versetrol Technology: Versetrol Technology is novel innovative technology that provides time controlled release for wide range of drug. In this technology drug is incorporated in lipophilic or hydrophilic matrix and that is than incorporated in soft gelatin capsule shell. This technology is versatile because depending on physiochemical properties of drug either emulsion or suspension can be developed. For lipophilic drugs suspension formulation is preferred while for hydrophilic drugs emulsion form is utilized. By applying combination of lipophilic and hydrophilic matrices desire release profile can be achieved [77].

17. The Ceform™ technology: It allows the production of uniformly sized and shaped microspheres of pharmaceutical compounds. This approach is based on "melt-spinning", which means subjecting solid feedstock (i.e., biodegradable polymer/bioactive agent combinations) to a combination of temperature, thermal gradients, mechanical forces, flow, and flow rates during processing. The microspheres obtained are almost perfectly spherical, having a diameter that is typically 150–180mm, and allow for high drug content. The microspheres can be used in a wide variety of dosage forms, including

tablets, capsules, suspensions, effervescent tablets, and sachets. The microspheres may be coated for controlled release with an enteric coating or may be combined into a fast/slow release combination [78][79].

18. Chronotopic® Technology: It is basically drug-containing core coated with an outer release-controlling layer. Both single and multiple-unit dosage forms such as tablets and capsules or mini tablets and pellets have been employed as the inner drug formulation.

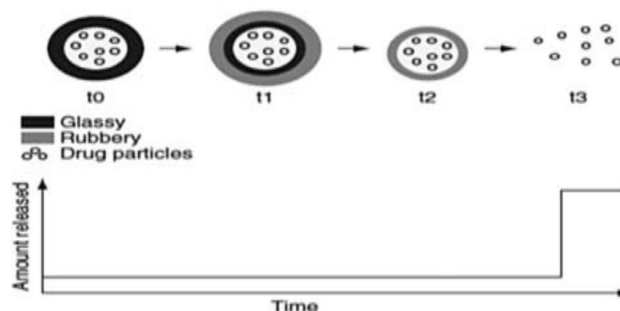


Figure 16: Chronotopic Technology

19. INNOHERB: In this technology, pellets are coated inside of the capsule. Desired active herbal compound converted into micro pellets or small beads. The coating of these carried out by semi permeable membrane to improve stability and mask taste/smell [80].

20. Covera-HS: Covera-HS is the first once-daily formulation of an antihypertensive/anti-anginal agent that uses an advanced tablet coating and a novel drug delivery system to mimic the body's typical 24 h circadian variations in blood pressure and heart rate. This unique delivery technology, called COER-24™ (Controlled-Onset-Extended-Release), was developed in conjunction with AlzaCorp. Covera-HS is the only controlled-release verapamil formulation that is currently approved with an indication for the management of both hypertension and angina pectoris. Covera-HS is designed for oral dosing at bedtime. Peak concentration of Covera-HS is delivered in the early waking hours, when blood pressure and heart rate are rise at their highest rate.

21. Oros® Technology: Chronset™ is a proprietary OROS® delivery system that reproducibly delivers a bolus drug dose in a time- or site-specific manner to the gastrointestinal tract. It is nothing but osmosis based system. The active pharmaceutical is kept in a reservoir surrounded by a Semipermeable

membrane laser drilled with a delivery orifice and formulated into a tablet. There are two layers in this tablet comprising of one drug layer and another osmotically active agent. Upon contact with GI fluid this osmotic agent changes its characteristic from non-dispensable to dispensable viscosity. As a result active pharmaceutical is pushed away through the channel due to pump effect of the osmotic agent. It is used generally for designing of extended release tablet^[81].

22. Magnetic nanocomposite hydrogen:

Magnetic nanocomposite of temperature responsive hydrogel was used as remote controlled Pulsatile drug delivery. Nanocomposites were synthesized by incorporation of superparamagnetic Fe₃O₄ particles in negative temperature sensitive poly (Nisopropyl acrylamide) hydrogels along with model drug. High frequency alternating magnetic field was applied, the beads oscillate within the matrix, creating compressive and tensile forces, and hydrogel temperature increases results into accelerated collapse of gel. This in turn acts as a pump to push an increased amount of the drug molecule out the matrix to produce on demand Pulsatile drug release from nanocomposite hydrogel. Also magnetic particle like magnetite, iron, nickel, cobalt and steel can also be incorporated^[82].

23. Microfabrication: These devices contain small reservoirs loaded with drugs and separated from outside environment by thin membrane. The active silicon-based microchip membrane is thin layer of gold. In order to release the drug the voltage need to be applied. The release mechanism is based on the electrochemical dissolution of thin anode membranes covering micro reservoirs filled with chemicals in solid, liquid or gel form. Here a solid-state silicon microchip that can provide controlled release of single or multiple chemical substances on demand. A study for release have been conducted with a prototype microchip using gold and saline solution as a model electrode material and release medium, and demonstrated controlled, Pulsatile release of chemical substances with this device^[83].

24. Timerx® Technology: It is hydrogel based controlled release device. This technology can provide from zero order to chrono therapeutic release. It can provide different release kinetic by manipulating Molecular interactions. The

authors claimed that the “molecular engine” replaces the need for complex processing or novel excipients and allows desired drug release profiles to be “factory set” following a simple formulation development process. Basically, this technology combines primarily xanthan and locust bean gums mixed with dextrose. The physical interaction between these components works to form a strong, binding gel in the presence of water. Drug release is controlled by the rate of water penetration from the gastrointestinal tract into the TIMERx gum matrix, which expands to form a gel and subsequently releases the active drug substance^[84].

25. DMDS Technology: DMDS (Dividable Multiple Action Delivery System) is designed to provide greater Dosing flexibility that improve product efficacy And reduces side effects. Traditional Controlled release tablet often lose their Controlled release mechanism of delivery once it broken. But DMDS technology allows tablet to be broken down in half so that each respective portion of the tablet will achieve exactly the same release profile as the whole tablet. This allows the patient and physician to adjust the dosing regimen according to the clinical needs without compromising efficacy^[85].

CONCLUSION

Currently, oral delivery of drug is still most preferable route of drug delivery due to the High patient compliance, ease in administration and flexibility in its formulations. Generally, sustained and controlled-release products provide a desired therapeutic effect, but fall short of diseases following biological rhythms, circadian disorders such as hypertension, osteoarthritis, peptic ulcer, asthma etc., which require chrono pharmacotherapy. Circadian rhythm of the body is an important concept for understanding the optimum need of drug in the body. There is a constant need for new delivery systems that can provide increased therapeutic benefits to the patients. Pulsatile drug delivery is one such system that, by delivering drug at the right time, right place and in right amounts, holds good promises of benefit to the patients suffering from chronic problems. A variety of systems like Time, Stimuli, Externally regulated Multiparticulate regulated Pulsatile thus designing of proper Pulsatile drug delivery will enhances the patient compliance, optimum drug delivery to the target site and minimizes the undesired effects. The approaches in this article

represent attempts conducted over the past decade to achieve Pulsatile release.

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