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Pulsatile Drug Delivery System: A Review

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ABSTRACT

In the recent years the pulsatile drug release systems are gaining growing interest. The pulsatile drug release where the drug is rapidly released after the well defined lag-time could be advantageous for many drugs or therapies. The sustained & controlled release devices are not applicable in some of the cases like the time-programmed administration of the hormones & many drugs. The living systems are the predictable dynamic resonating systems which require different amounts of drug at the expected times within the circadian cycle. The pulsatile drug delivery system has fulfilled this requirement. This system is such a system where the drug is released suddenly after the well-defined lag time or the time gap according to the circadian rhythm of the disease states. No drug is released from the device within this lag time. This method is good for the drugs with the extensive first pass metabolism & targeted to the specific site in the intestinal tract. The current article focuses on the necessities of pdds, diseases requiring PDDS, classification of pulsatile drug delivery system, current situation and future scope& marketed technologies of pulsatile drug delivery system.

Keywords: Pulsatile drug delivery system, lag time, first pass metabolism.

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INTRODUCTION

With the advancement of the technologies in the pharmaceutical field the drug delivery systems have drawn an increasing interest over the last few decades. Now a day, the emphasis of the pharmaceutical galenic research is turned towards the more efficacious drug delivery systems development. With the already existing molecule rather than going for the discovery of new drug because of the inherent problems posed in the process of drug discovery & development. The delivery of drug is meant for getting the simple chemical absorbed predictably from the gut or from the site of the injection traditionally. The typical pattern of the drug release is shown by the oral controlled release system in which the concentration of drug is maintained for the prolonged period of time [sustained release] in the therapeutic window thereby ensuring the sustained therapeutic action. The goal of second generation drug delivery has been the perfection of the continuous constant rate delivery of the bioactive agents. In their requirement or the response to the drugs, however the living organisms are not Zero Order. They are predictable, resonating, dynamic circadian cycle which will minimize the undesired drug effects & maximize the desired effects. The efforts have been made to design the drug delivery systems till the early 90's, which will release the drugs at the fairly constant rate. In delivering the drug molecule these systems turn out to be one of the most successful systems. Still for many of the drug's use of such systems is not suitable because of the number of reasons. In the cases, where the drug is subjected to the large metabolic degradation this is particularly true. Due to first pass effect in the bioavailability of the drug there will be reduction because the gradual release can result in the greater degradation. Secondly, short half life drugs need to be administered repeatedly, which would results in the non-compliance of the patient. Where the drug is given in the sustained release dosage form in case of the chronic treatment, the continuous exposure of the drug to the body may lead to the adverse effects. For example, the chronic treatment is required for the diabetes mellitus with the sustained release formulations of the drugs like the sulfonylurea which will damage the pancreas earlier than the corresponding immediate release dosage form .Lastly, since the drug effect decreases with the time at constant drug level, in addition the drug toxicity increases with the time when drug levels are held constant the drugs which exhibit the tolerance should not be delivered at the constant rate. In such cases it is preferable to opt from a dosage form which will provide at the particular time point only a desired concentration of the drug. Now days, the concept of chronopharmaceutics has emerged wherein, the research is devoted to the design and the evaluation of the drug delivery system that releases the therapeutic agents at the rhythm that ideally matches the biological

requirement of the given therapy of the disease. In some diseases where the constant drug levels are not preferred but there is need of the pulse of the therapeutic concentration in the periodic manner acts as the push for the development of the pulsatile DDS. Immediately after the predetermined off release period there is the rapid & transient release of the certain amount of the drug molecules within the short time period in these systems. For the pulsatile drug delivery system, the various techniques are available like micro flora activated systems, pH dependent systems, time dependent systems, which can be designed as per the properties of the drug molecule & physiology of the disease. [1-6]

Advantages of the Pulsatile drug delivery systems

1. The Targeting of the drug to the specific site like the colon {in case of the ulcerative colitis} can be achieved.
2. At the site of action it provides the constant drug levels and the peak-valley fluctuations is prevented.
3. The drugs having the chronopharmacological behavior this system is beneficial where the night time dosing is required and for the drugs that have high first pass effect.
4. For the drugs that cause the gastric irritation {For e.g. NSAIDS} the protection from the gastric environment is essential or the drugs that get degraded in the gastric medium {For e.g. peptide drugs} so the pulsatile drug delivery system which is enteric coated can be the best option.
5. For the extended day time or night time activity this system can be used.
6. They reduce the cost, dose frequency and dose size, which ultimately reduces the side effects there by the patient compliance is improved.
7. To prevent the continuous presence of some drugs {E.g. salbutamol sulphate} these systems are helpful that produces the biological tolerance and thus they increase their therapeutic effect.
8. The hormones such as renin, aldosterone and cortisol etc, in the blood their levels may alter with the circadian rhythms therefore, through this system the drug delivery suits the circadian rhythms of the functions of the body or the diseases.[7-8]

Limitations

1. In single unit pulsatile drug delivery system there is in vivo variability
2. In case of Multiparticulate drug delivery system there is multiple manufacturing steps.
3. There is no possibility of immediate withdrawal of drug.
4. In case of child and elder patients the drug dose manipulation is not possible.

5. Drug loading capacity is low and release of drug is incomplete. [9]

Biological rhythms

There are three types of Biological rhythms in our body. They are:

i. Circadian ii. Ultradian iii. Infradian

i. The Circadian

Franz Halberg from the Latin circa coined the term circadian, meaning about and dies meaning day.

ii. The Ultradian

The shorter duration oscillations are termed as ultradian. { having more than one cycle per 24 hrs}

iii. The Infradian

The Oscillations which are longer than 24 hours {less than one cycle per day}

At all levels of a biologic organization the ultradian, circadian & infradian rhythms coexist.[10-11]

NECESSITIES OF PULSATILE DRUG DELIVERY SYSTEM

1. **The First pass metabolism**

The drugs like salicylamide and beta blockers undergo the extensive first pass metabolism and to saturate the metabolizing enzymes in order to minimize the pre-systemic metabolism they require the fast drug input. Thus, the sustained /constant oral method of the delivery would result in the reduced oral bioavailability.

2. **The Biological tolerance**

By the decline in the pharmacotherapeutic effect of the drug the drug plasma profiles are often accompanied. For eg, the biological tolerance of the transdermal nitroglycerin, salbutamol sulphate.

3. **The Special chronopharmacological needs**

The circadian rhythms are well established in certain physiological functions. It has been recognized that during the specific time periods of the 24 hour day many symptoms and onset of disease occur. For e.g., the angina pectoris and asthma attacks are most frequently in the morning hours.

4. **The Local therapeutic need**

The delivery of compounds to the site of inflammation with no loss due to absorption in the small intestine is highly desirable to achieve the therapeutic effect and to minimize side effects, for the treatment of local disorders such as inflammatory bowel disease,

5. **The Gastric irritation or drug instability in gastric fluid**

For the drugs that undergo the degradation in the gastric acidic medium {eg, peptide drugs} irritate the gastric mucosa {NSAIDS} or induce the nausea and vomiting the protection from the gastric environment is essential. [8, 12]

CLASSIFICATION OF PULSATILE DRUG DELIVERY SYSTEM

I. The Time controlled pulsatile release system

It can be classified as the single unit {For e.g., capsule or tablet} or multiple unit systems.

The single unit system

The capsular Systems:

Various single unit capsular pulsatile drug delivery system have been developed. The general design of such systems consists of the insoluble capsule body housing the drug and the plug. After the predetermined time lag the plug is removed due to the dissolution, erosion or swelling. The pulsincap system is the example of such system that is made up of the water-insoluble capsule body that is filled with the drug formulation. The body is closed at the open end with the swellable hydrogel plug. The plug swells, pushing itself out of the capsule after the time lag, upon contact with the dissolution medium or the gastro-intestinal fluids. It is followed by the spontaneous release of drug. The time lag can be controlled by manipulating the dimension and the position of the plug. The plug material consists of the insoluble but permeable and swellable polymers, for e.g. the enzymatically controlled erodible polymer for e.g: pectin, the erodible compressed polymers {For e.g: polyvinyl alcohol hydroxypropylmethyl cellulose}, congealed melted polymers {For e.g: glycerylmonoole, saturated polyglycolated glycerides}. In the animals and the healthy volunteers these formulations are well tolerated and there have been no reports of the gastrointestinal irritation. Hence, there was the potential problem of the variable gastric residence time, but it was overcomed by the enteric coating system to allow its dissolution only in the higher pH region of the small intestine.[13-14]

The Pulsatile System Based On Osmosis

The Port Systems

This system consist of the gelatin capsule which is coated with the semi permeable membrane {For e.g: cellulose acetate} the housing an insoluble plug {For e.g: lipidic} and an osmotically active agent along with the formulation of the drug. The water diffuses across the semi permeable membrane on contact with the aqueous medium which results in the increased inner pressure that ejects the plug after the lag time. The time lag is controlled by the thickness of the semi permeable membrane. An osmotically driven capsular system was developed in order to deliver the drug in the liquid form. In this system into the highly porous particles the liquid drug is absorbed which

releases the drug through the orifice of the semi permeable capsule which is supported by an expanding osmotic layer after dissolving of the barrier layer.[15-16]

The Delivery by the Series of Stops

This system is described for implantable capsules The osmotically driven delivery capsule contains the therapeutically active agent and water-absorptive osmotic engine which is separated by the slider partition to deliver the drug in the pulsatile manner through the orifice. The needed lag time for the pulsatile delivery is achieved by the series of the stops placed along the capsules inner wall which obstructs its movement. To deliver the next batch of the drug the partition is forced as above the threshold level the hydrostatic pressure rises. The intensity of pulse is controlled by their position along the longitudinal axis and the number of stops.[17]

The single unit systems delivery by solubility modulation

For the pulsed delivery of the variety of drugs, this system contains the solubility modulator. For the delivery of the salbutamol sulphate the system was developed. Its composition contains the modulating agent {sodium chloride} and the drug {salbutamol sulphate}. The amount of sodium chloride was such that it was less than the amount that was needed to maintain the saturation in the fluid which enters the osmotic device. The pulsed delivery is based on the drug solubility. The modulating agent can be the organic salt, inorganic salt, solid organic acid.[18]

The system based on the expandable orifice

This device is in the form of the capsule from which the drug is delivered by a capsule's osmotic infusion of the moisture from the body. There is an orifice consisting of the elastic material on the capsule's wall. It is so small that the flow of the drug through the orifice is nearly zero under the relaxed condition. The pressure is developed inside the shell when the elastic wall is stretched. The orifice expands sufficiently from time to time, consequently to allow the release of the drug in the pulsatile manner.[14]

The delivery by the reservoir systems with erodible or soluble barrier coatings

The drug release is controlled by the dissolution or the erosion of the outer coat which is applied on the core containing the drug in such systems. The time dependent release of the active ingredient can be obtained by optimizing the thickness of the outer coat. This system is another class of the reservoir type pulsatile systems with the barrier layer which erodes or dissolves after the specific lag time followed by the burst release of a drug from the reservoir core. Generally in this, the lag time is controlled by thickness of the coating layer. A chronotropic system which consists of the drug containing the core layered with the hydroxy propyl methyl cellulose and the enteric coating of the top layer the lag time before the release of the drug will be dependent upon

the thickness and the viscosity grade of the hydroxy propyl methyl cellulose layer. in this type of system since the drug release mechanism is dissolution, that's why a high degree of the drug solubility relative to the dose of a drug is essential for the drugs rapid release after the lag period. The various grades of the hydroxy propyl methyl cellulose and Eudragit {acrylates} polymers have been studied, to in an attempt to deliver a drug to the various sites in the gastrointestinal tract due to their eroding properties and solubility. On the slow dissolution behavior of the high viscosity polymers the formulation is dependent. It consists of a mini tablet with therein dispersed the drug substance which is coated with a high viscosity polymer {HPMC 40000} and an outer enteric coating. A outer film protects the system from the fluid in the stomach and upon entering in the small intestine it dissolves. When the system is transported through the small intestine the hydroxy propyl methyl cellulose layer delays the drug release for about 3-4 hours. The expected behavior & release profile of the erodible /swellable reservoir systems for the oral pulsatile delivery.[15, 19]

B) The Multiparticulate Systems

These systems are the reservoir type of the devices with the coating, which either changes its permeability or the ruptures. Over the sugar seeds the drug is coated, these granules to form the tablet may be then packaged in the capsule or compressed with the additional excipients. Before coating the active pharmaceutical ingredient may also be blended or granulated with the polymers to provide an additional level of the control. Hence, in this type of system the drug loading is low due to need of excipients is higher.[20]

The pulsatile delivery by change in membrane permeability

These systems are designed when the sigmoidal release pattern is desired therapeutically beneficial for the timed release and colonic drug delivery. By change in the permeability of polymeric coating layer the drug release is achieved in the presence of the certain counter ions of the surrounding media, on the basis of this The Narisawa et al, developed a device capable of the pulse-release depending on the change in the diffusion properties of the Eudragit RS. They analyzed that a core of the theophylline coated with the Eudragit RS in the pure water has shown very slow release but significant increase in the release rate was found when in the organic acid solution containing the malic acid, tartaric acid, glutaric acid succinic acid or citric acid the microcapsules were immersed. The reason behind it was that the higher hydration of the film containing the quaternary ammonium groups in the polymer chain was not affected by the succinic acid suggesting that the quaternary ammonium groups of the Eudragit RS are essential to produce a unique drug release profile. Based on the permeability changes the release profile of the systems depend strongly on the physicochemical properties of the drug and its interaction with the

membrane. Therefore with this system the pulsatile release profile may be obtained for some of the particular drug molecules in a specific form but it cannot be applied generally to all the drugs.[21]

The pulsatile system based on the rupturable coating

It consists of the outer release controlling the water insoluble but permeable coating subjected to the mechanically induced rupture phenomenon. Recently the various systems based on the tablet core and hard gelatin capsules were described all coated by the inner swellable and outer rutpurable layer. The rupture film may be attained by including the effervescent, swelling or osmotic additives in the reservoir. The Bussemer et al had worked on the pulsatile system with the rupturable coating on the drug present in a hard gelatin capsules. With the swelling layer these capsules were first coated and then with the insoluble but water-permeable outer coating. When immersed in the release media this coated capsule could take up the media at the constant rate up to a point when the outer coating would rupture due to the pressure caused by the swelling layer. By increasing the swelling layer it could be concluded that the lag time could be shortened. By increasing the outer coating however, the lag time could be prolonged. It was also observed that the addition of the hydroxy propyl methyl cellulose to the outer coating shortens the lag time. For the biologically active material the pharmaceutical implant was developed, an excipient comprising at least one water soluble material and above which a polymer film coating adapted to rupture at a predetermined period of time after the implantation. The bilayer film coating forms an impermeable barrier to the drug in one form. The degree of the access of physiological film to the inner film is controlled by the insoluble outer film. A film coating comprises the mixture of ethyl cellulose and the copolymer of the glycolic and lactic acids is used. As the ethyl cellulose is the insoluble polymer when the polylactic glycolic acid {PLGA} polymer in the film hydrolyses the film becomes porous and allows the drug release. The rate of hydrolysis of the polylactic glycolic acid {PLGA} depends on the ratio of a lactic acid to glycolic acid in a polymer.[22-23]

II. The **Stimuli induced pulsatile release system**

A. The inflammation-induced Pulsatile Release

The inflammation takes place at the injured sites. From these inflammation-responsive cells the hydroxyl radicals are produced during inflammation. The Yui and co-workers focused on the inflammatory induced hydroxyl radicals and designed a drug delivery system which responded to the hydroxyl radicals and are degraded in the limited manner. They used the hyaluronic acid (HA) which is degraded specifically by the free radicals or the hyaluronidase. In the normal state of health the degradation of the hyaluronic acid via the hyaluronidase is very low. However the degradation via the hydroxyl radicals is usually dominant and rapid when the H is injected at the

inflammatory sites. Hence, it is possible to treat the patients with the inflammatory diseases like the rheumatoid arthritis by using the anti-inflammatory drugs incorporated hyaluronic acid gels as the new implantable drug delivery system.[24]

B. The temperature induced systems

The thermo-responsive hydrogel systems have been developed for the pulsatile release. In this system the polymer undergoes the deswelling or the swelling phase in response to the temperature which modulate the release of drug in the swollen state. The indomethacin pulsatile release pattern in the temperature ranges between 20^{0C} and 30^{0C} was developed by the Y.H. Bae et al by using the reversible swelling properties of the copolymers of the butyrylacrylamide and N-isopropylacrylamide.[25-26]

C. The pH sensitive drug delivery system

This type of the system contains 2 components 1 is of the immediate release type and another one is the pulsed release which releases the drug in response to the change in the pH. The advantage has been taken of the fact in case of the pH dependent system that there exists different pH environment at different parts of the gastrointestinal tract. The drug release at the specific location can be obtained by selecting the pH dependent polymers. Examples of the pH dependent polymers include the sodium carboxy methylcellulose, Eudragit E-100, cellulose acetate phthalate, polyacrylates.[27]

III. The chemical stimuli induced pulsatile systems

This system was divided into 3 subparts and is discussed below,

A. The glucose-responsive Insulin Release Devices

There has been much interest in the development of stimuli-sensitive delivery system that releases therapeutic agents in the presence of the specific enzyme or the protein. In this system there is drug release after the stimulation by any of the biological factors like the enzyme, pH or any other chemical stimuli. This novel type of the glyco-sensitive gel may have the potential utilities in the self-regulated drug-releasing systems as well as in the other applications such as the actuators, regulators and the separation systems with the glyco-sensitivity, For the treatment of the diabetic patients the fabrication of the insulin delivery system. Delivering insulin is different from delivering the other drugs, since insulin has to be delivered in an exact amount at the exact time of need. For this purpose many devices have been developed and all of them have the glucose sensor built into the system. In a environment which is glucose-rich such as the bloodstream after the meal the oxidation of the glucose to the gluconic acid catalysed by the glucose oxidase can lower the pH to the approx 5.8. In glucose sensing this enzyme is probably the most widely used and

makes possible to apply the different types of the pH-sensitive hydrogels for the modulated delivery of insulin. This change in the pH induces the swelling of the polymer which results in the release of insulin. By virtue of its action the insulin reduces the glucose level in the blood and consequently the gluconic acid level also gets decreased and the system turns to a deswelling mode thereby decreasing the insulin release.[28]

B. Drug release from intelligent gels responding to antibody concentration

There exist numerous kinds of bioactive compounds in the body. The novel gels were developed recently which responded to the change in the concentration of the bioactive compounds to alter their deswelling /swelling characteristics. To the antigen-antibody complex formation the special attention was given, as the cross-linking units in the gel since such interactions are very specific. By utilizing the difference in the association constants between the polymerized antibodies and the naturally derived antibodies towards the specific antigens the reversible gel deswelling/ swelling and the changes occurs of the drug permeation.[29]

IV. External stimuli pulsatile release

This system was divided into 3 subparts and is discussed below.

A. Micro Electro Mechanical Systems [MEMS]

This micro fabricated device has a ability to store and release the multiple chemical substances on demand by the mechanism devoid of moving its parts. The digital capabilities of the Micro Electro Mechanical Systems may allow the greater temporal control over the release of drug as compared to the traditional polymer-based systems. The microchip is another development in the Micro Electro Mechanical Systems technology. The microchip consists of a array of the reservoirs that extend through the electrolyte-impermeable substrate. From silicon the prototype microchip is made and contains the number of the drug reservoirs each of the reservoir is sealed at one end by the gold membrane of the material which is thin that serves as an anode in an electrochemical reaction and dissolves in an electrolyte solution when an electric potential is applied to it. With any of combination of the drug or the drug mixtures in any form {i.e. gel, solid or liquid,} the reservoirs are filled. An electric potential is applied between the anode membrane and the cathode when the release is desired, within 10-20 seconds the gold membrane anode dissolves and allows the drug in the reservoir to be released. These electric potential causes the oxidation of the anode material to form a soluble complex with the electrolytes which then dissolves allowing the release of the drug. From the microchip the complex release patterns {such as pulsatile release and simultaneous constant} can be achieved. To control both the release time and release rate the microchip has the ability.[13]

B. Magnetically Induced Pulsatile Release

To regulate a drug delivery from the polymer matrix by use of an oscillating magnetic was one of the first methodologies investigated to develop a externally controlled drug delivery system. From the incorporated materials such as the nickel, cobalt, magnetite, iron, etc the magnetic carriers receive the response to the magnetic field. The magnetic carriers must be biocompatible, water-based, non-toxic and non-immunogenic for the biomedical applications. A mechanistic approach behind the strategy is based on slowing down the movement of the oral drugs in the gastrointestinal system through the magnetic attraction. By filling the additional magnetic component into the tablets or capsules this is possible. At the specific positions the speed of the travel through the stomach and intestines can then be slowed down by the external magnet thus changing the timing or the extent of the drug absorption into the stomach or intestine.

C. The electro responsive pulsatile release

The combination of the developments in the various technologies such as the micromachining and microelectronics as well as the potential need for the chronotherapy has currently assisted the development of the drug delivery technologies that are electronically assisted. These technologies include iontophoresis, infusion pumps and sonophoresis. In the literature the several approaches have also been presented describing the preparation of the electric stimuli-responsive DDS by using the hydrogels. Kishi et al. had developed an electric stimuli induced drug release system using the electrically stimulated deswelling /swelling characteristics of the polyelectrolyte hydrogels. They utilized the chemomechanical system which contained a drug model within the polyelectrolyte gel structure. This gel exhibited the reversible shrinking/ swelling behavior in response to a on–off switching of the electric stimulus. Therefore the drug molecules within a polyelectrolyte gels might be squeezed out from a electric stimuli-induced gel contraction along with a flow of the solvent. Poly {sodium acrylates} microparticulate gels containing the pilocarpine as a model drug were prepared to realize this mechanism.[30]

DISEASES REQUIRING PULSATILE DELIVERY

The diseases have predictable cyclic rhythms & that the timing of the medication regimens can improve the outcome in selected chronic conditions have been revealed in the recent studies. Various diseases which are required to be formulated as Pulsatile drug delivery system like, cancer, cardiovascular diseases, hypercholesterolemia, diabetes, duodenal ulcer, asthma, arthritis, colonic delivery and the neurological disorders. During the hepatic cholesterol synthesis the circadian rhythm occurs. Therefore as compared to during the daylight the cholesterol synthesis is generally higher during the night. The maximal production occurs early in the morning that is 12

hours after the last meal. The studies with the HMG CoA reductase inhibitors have suggested that than the morning dosing the evening dosing was more effective. In humans, the circadian rhythm regulates many of the body functions, viz., Physiology, hormone production, behaviour, sleep patterns, metabolism, etc. In case of the cardiovascular diseases the BP is at its lowest & rises steeply during the early morning period during the sleep cycle. The platelet agreeability is increased & fibrinolytic activity is decreased in the morning which leads to the state of the relative hypercoagulability of the blood. In the blood sugar level the circadian increases after the meal has been observed in the diabetes mellitus. The circadian variations are seen in the DOPA level in the afternoon in case of the Attention deficit syndrome.

The human & animal studies suggest that the chemotherapy may be more effective & less toxic if the cancer drugs are administered at the times that are carefully selected that take the advantage of the tumour cell cycles while less toxic to the normal tissue. In the GI ulcer many of the functions of the GI tract are subject to the circadian rhythms. At the night the gastric acid secretion is highest, while the gastric & small bowel motility & the gastric emptying at the night are all slower. The drug disintegration, drug dissolution & absorption may be slower the pulse release is curative when the gastric motility & emptying are slower during the night time. The asthma is one such disease where the pulsatile drug delivery system can be useful. A circadian change is seen in the normal function of the lung the airway resistance increases progressively at the night in the asthmatic patients. The chronotherapies have been studied with the oral corticosteroids, theophylline & B2- agonists for asthma. The preferred absorption site is the colon for oral administration of protein & peptide drugs due to the relatively low proteolytic enzyme activities in the colon. The Colon-Specific drug delivery system should prevent the release of drug in the stomach & small intestine & affect an abrupt onset of the drug release upon the entry into colon. The time dependent delivery has also been proposed as the means of the targeting the colon.[27, 31-38]

MARKETED TECHNOLOGIES OF PULSATILE DRUG DELIVERY SYSTEM

Orbexa®

The Orbexa technology is the multiparticulate system that enables the high drug loading & is suitable for the products that require the granulation. The Eurand's Orbexa technology produces beads of the controlled size & density using the extrusion, spheronization & granulation techniques. These beads provide the higher drug concentration than the other systems can be coated with the functional polymer membranes for the additional control of the release rate are flexible & are suitable for the use with the sensitive materials, such as the enzymes. The Eurand's Orbexa technology can be used for the delayed release, site-specific delivery, gastric protection,

sustained release, complex release pattern, pulsatile delivery, separation of the incompatibles & combination products. The Orbexa beads can be filled into the capsules or the single-dose sachets.[39-40]

Geoclock®

The SkyePharma has developed the new oral drug delivery technology. The Geoclock®, in the form of chronotherapy-focused press-coated tablets. The Geoclock® tablets have an active drug inside the outer tablet layer which consists of the mixture of the hydrophobic wax & brittle material in order to obtain the pH-independent lag time prior to the core drug delivery at the predetermined release rate. This approach of dry coating is designed to allow the timed release of the both immediate release & slow release active cores by releasing first the inner tablet, after which time the surrounding outer shell disintegrates gradually. The Geoclock® technology also has applications for the improved release of colonic drug delivery as well as for multiple pulse drug delivery to deliver doses of a drug at specific times throughout the day, in addition to the controlled release. Using the SkyePharma's proprietary the Geoclock™ technology, Lodotra™ took the form of the specially formulated tablet, which ingested once did not release the active ingredient prednisone, until the approximately 4 hours later. The Lodotra™ has been designed so that the maximum plasma levels are reached 6 hours after the intake. This enables the patient to swallow a tablet at 10 p.m. before going to the sleep with the dose of the prednisone not being released until the 2 a.m. & reaching the maximum plasma levels at the 4 a.m. which is regarded as the optimal timing to relieve the pain & stiffness on waking. This nighttime release formulation is suited especially to the treatment of the early morning stiffness which is associated with the rheumatoid arthritis caused by the marked release of the inflammatory cytokines including interleukin-6 [IL-6] in the early hours of morning.[41]

Uniphyl®

The Uniphyl [theophylline, anhydrous] tablets in the controlled-release system allow the 24 hours dosing interval for the patients. After oral administration the Uniphyl administered in the fed state is completely absorbed.

PULSYS™

The MiddleBrook Pharmaceuticals, Inc. has developed the delivery technology called PULSYS, which enables the pulsatile delivery or the delivery in the rapid bursts of the certain drugs. The technology provides the absorption & prolonged release of the drug. The company's PULSYS product MOXATAG tablets [amoxicillin extended-release] 5 mg are used for the treatment of the tonsillitis /pharyngitis secondary to the *Streptococcus pyogenes*, commonly known as the strep

throat for the pediatric patients age 12 and older & adults patients. The MOXATAG's once-daily extended-release tablet consists of the 3 components, 1 immediate release & 2 delayed-release components. The 3 components are combined in the specific ratio using its PULSYS technology to prolong the release of the amoxicillin from the MOXATAG compared with amoxicillin which is immediate-release. [42-44]

Minitabs®

The Eurand's Minitabs are the tiny [2 mm x 2 mm] cylindrical tablets coated with the functional membrane to control the drug release rate. The Eurand Minitabs contain the gel-forming excipients that control rate of drug release. The additional membranes may be added to the further control of the release rate. Into capsules the tablets are filled allowing the combination of the multiple drugs &/or multiple release profiles in the same dosage form. A Eurand Minitabs can be formulated as the matrix tablets prior to the further coating. The Eurand Minitabs can also be used as a sprinkle on the food. The Eurand Minitabs combine the simplicity of the tablet formulation with the sophistication of the multiparticulate systems, suitable for the high drug loading & can be used as the sprinkle for geriatric & pediatric patients who have difficulty in swallowing the tablets. [40, 45]

The Pulsincap™ technology

The Pulsincap was developed by the R.R. Scherer International Corporation [Michigan]. This device consists of the non-disintegrating half capsule body sealed at the open end with the hydrogel plug that is covered by the water-soluble cap. With an enteric polymer the whole unit is coated to avoid the problem of the variable gastric emptying. When this capsule comes in contact with the dissolution fluid it swells & after the lag time the plug pushes itself outside the capsule & rapidly releases the drug. Another formulation approach was in the form of the granule or bead with the 4-layered spherical structure which consists of a drug, core, swelling agent [For e.g., carboxy methyl cellulose sodium or the sodium starch glycolate] & an outer membrane of the water-insoluble polymer [For e.g., Eudragit® RL, Ethyl cellulose]. The penetration of the gastrointestinal fluids through the outer membrane causes an expansion of the swelling agent. A resulting stress due to the swelling force leads to a destruction of the membrane & the subsequent rapid drug release. For designing the hydrogel plug the polymers used were various viscosity grades of the HPMC, polyvinyl acetate, poly ethylene oxide polymethyl methacrylates. Another new approach was the ETP tablets [Enteric-coated, Timed-release, Press-coated tablets]. These tablets were developed by the coating of enteric polymer on timed-released press-coated tablets composed of an outer shell of the HPC [Hydroxyl Propyl Cellulose] & the core tablets containing the diltiazem hydrochloride as the model drug. The Patel & Patel developed the modified

Pulsincap device containing the diclofenac sodium to target the drug in the colon. This is a time-dependent & site-specific formulation that is by administering the formulation at the bed time, the symptoms that are experienced early in the morning are avoided. After administering the single dose by continuously releasing the medication over an extended period of time this therapeutic effect is prolonged. The objective of the study was to explore the time- & pH-dependent controlled drug delivery of the Diclofenac Sodium by using the pulsincap system. [46-49]

Three-dimensional printing®

The 3DP [3-dimensional printing] is the novel solid free form fabrication technology that has been applied to the fabrication of the complex pharmaceutical drug devices, or the 3DP [3-dimensional printing] is the RP [rapid prototyping] technology. The Prototyping involves the constructing specific layers that use the powder processing & liquid binding materials. The reports in the literature have highlighted the various advantages of the 3-dimensional printing system over the other processes in enhancing the pharmaceutical applications these include the new methods in the development, design, commercialization & manufacture of the various types of solid dosage forms. For eg, 3-dimensional printing technology is flexible in that it can be used in the applications linked to the linear DDS, oral fast disintegrating delivery systems, colon-targeted DS, time-controlled and pulse release delivery systems floating delivery systems, as well as the dosage forms with the multiphase release properties & implantable drug delivery system. In addition the 3-dimensional printing can also provide the solutions for resolving the difficulties relating to the delivery of the proteins & peptides, poorly water-soluble drugs, potent drugs &highly toxic drugs & controlled release of the multidrugs in the single dosage forms.

The 3-dimensional printing has some advantages over the conventional compressing & other RP technologies in fabricating solid drug delivery system, due to its flexible & highly reproducible manufacturing process. This enables 3-dimensional printing to be further developed for the use in pharmaceutics applications. There are some problems that limit the further applications of the system, such as the selection of the suitable excipients & the pharmacotechnical properties of the 3-dimensional printing products. To overcome these issues further developments are therefore needed so that the 3-dimensional printing systems can be successfully combined with the conventional pharmaceutics. The limitations of the technology as relating to the pharmaceuticals have been addressed & prototype dosage forms have been fabricated. The resolution of the 3-dimensional printing tablets was found to depend on the particle size & liquid migration during the printing & drying. The surface finish of the 3-dimensional printing tablets was enhanced by the uniaxial pressing. The migration inhibiting additives were effective in the limiting transport. Both

the ethanol-based solutions & aqueous solutions showed the decrease in the migration on the order of 20% when the appropriate powder bed additives were introduced. The migration was also decreased by the pre-printing barriers to confine the secondary printed drug solutions. The low dosage forms were fabricated with as little as the 2.3 nanograms. The lower dosages are expected upon the dilution of the initial drug solution. The printing forms with the high dosage are limited by the drug solubility limits, powder void volume & filling efficiency. The complex oral dosage forms were fabricated with the 3-dimensional printing to show the lagged release, double release, extended release & zero-order release. The release properties, such as the lag time & release rate were manipulated by varying the printing parameters. The dual-release & the zero-order-release forms were fabricated using the surface erosion/ degradation system based on the Eudragid RL100, Hydroxy Propyl Methyl Cellulose & Lactose. The erosion rate constants were used to model release from the tablets with the non-uniform drug distributions. The diclofenac & chlorpheniramine dual-release tablets were designed with the 3 drug regions & the dissolution of the tablets closely followed the model, exhibiting two onsets. The two types of the zero-order tablets were invented & fabricated by the 3-dimensional printing. These contained the drug concentration gradients designed to complement the volumetric non-uniformity of the eroding shells. The 3 formulations showed the constant release of the diclofenac sodium over 1–7 hours [9.6 mg/hr], 1–15 hours [6.8 mg/hr] & 1–36 hours [2.5 mg/hr].[50-52]

CODAS® [Chronotherapeutic oral drug absorption system]

The immediate release of drug is undesirable in certain cases. For the variety of reasons a delay of the drug action may be required. The Chronotherapy is an example of when the drug release may be programmed to occur after the prolonged interval following the administration. To achieve this prolonged interval, the Elan Drug Technology developed CODAS® technology. Many advantages of the CODAS® technology include the delivery profile designed to the compliment circadian pattern, an extended release delivery system, controlled onset, posture & food, rate of release essentially independent of the pH, the "sprinkle" dosing by opening the capsule & sprinkling the contents on the food, reduction in the effective daily dose & drug exposure, GI tract targeting for the local effect & reduced the systemic exposure to achieve the target profile. The Verelan® PM uses the proprietary CODAS™ technology which is designed for the bedtime dosing, incorporating the 4-5 hours delay in the delivery of drug. The controlled-onset delivery system results in the maximum plasma concentration [C_{max}] of the verapamil in the morning hours. These pellet-filled capsules provide for the extended release of the drug in the GI tract. The Verelan® PM formulation has been designed to initiate the release of the verapamil 4-5 hours after the ingestion.

This delay is introduced by the level of the non-enteric release-controlling polymer applied to the drug-loaded beads. The release-controlling polymer is the combination of the water soluble & water insoluble polymers. The water soluble polymer slowly dissolves, & the drug diffuses through the resulting pores in the coating as the water from the GI tract comes into the contact with the polymer-coated beads. The water insoluble polymer continues to act as the barrier maintaining the controlled release of the drug. The rate of release is essentially independent of food, pH & posture. The multiparticulate systems, such as Verelan® PM, have been shown to be independent of the GI motility.[53-55]

DIFFUCAPS® technology

The variations in pH throughout the gastrointestinal tract affect the solubility & absorption of certain drugs. This dependency of pH can cause a problem particularly when developing the controlled or sustained release formula. The carvedilol & dipyridamole are the drugs that are soluble in acidic conditions of the stomach but they are insoluble in the slightly alkaline /neutral conditions of intestine where the absorption of the active drug is ideal. The particular concerns are the weak basic drug compounds that are insoluble at the pH greater than 5.The Eurand's Diffucaps® technology facilitates the development & commercialization of the novel, controlled-release delivery systems for the once- or twice-daily dosing of the single drugs or combinations of drug that exhibit the extreme pH-dependent solubility profiles or /and are poorly soluble in the physiological fluids. Specifically this proprietary technology has been developed for the weak, basic drugs & involves the incorporation of the pharmaceutically acceptable organic acid or the crystallization-inhibiting polymer onto the inert cores & coating the drug-layered beads with the proprietary functional polymers. The formulations using an acid core ensure that at all times the acidic environment surrounds the drug thereby producing the soluble drug in an in vivo environment where it would otherwise be insoluble. The Diffucaps® is the multiparticulate bead system comprised of the multiple layers of the drug, excipients & release-controlling polymers. The beads contain the layer of the organic acid or the alkaline buffer to control the solubility of the drug by creating an optimal pH microenvironment for the drugs that exhibit the poor solubility in the intestinal pH, in the environments with pH greater than 8.0 or in the physiological fluids. The Diffucaps® beads are < 1.5 mm in diameter & can be filled into the capsules or are compressed into the orally disintegrating tablets. In addition, for the patients who experience the difficulty in swallowing the tablets or capsules the Diffucaps® products are produced in the capsules that allow the capsules to be opened & the contents used as the sprinkle on foods providing the flexible dosage form. The flexibility of the Diffucaps® system allows for the easy adjustment of the release

profile & dosing strength to achieve the targeted in vivo results. This flexibility simplifies the dose-ranging studies for the drug development partners involved in the clinical testing because the beads can be encapsulated separately to create the separate study arms. The Eurand's Diffucaps® technology is used in the several currently marketed products & in the novel products in the clinical development. The Diffucaps® multiparticulate bead system enabled the development of the formulation with an initial release of a drug for the quick onset of action to maintain the consistent plasma levels throughout the day. The AMRIX is available in the 2 dose-proportional strengths 15 & 30 mg capsules. This illustrates an advantage of the Diffucaps® technology-multiple product strengths can be developed readily by using the differing amounts of the drug-layered beads contained in the final capsule dosage form. The Diffucaps® technology created the delayed release capsule that achieves the peak plasma levels in the AMRIX when the risk of patient is highest & continued maintenance throughout the day. The advantages of this multiparticulate system are its suitability for the drugs exhibiting poor solubility in the lower intestinal pH, in the environments with the pH above 8.0 or in the physiological fluids, where it can provide the dosage strength flexibility & the required PK profile give the optimal release profiles for the single drugs & combinations of drug & can minimize the food effects. To enhance the drug solubility in the gastrointestinal tract the Diffucaps® drug release system can also be used in combination with other Eurand technologies.[6, 56-59]

IPDAS®

The IPDAS [Intestinal protective drug absorption system] is the new oral drug delivery approach that is applicable to the GI [gastrointestinal] irritant drugs including the NSAID [nonsteroidal anti-inflammatory] drug class. To confer the advantages of the multiparticulate technology in a tablet dosage form the IPDAS® delivery system can also be employed. The IPDAS® technology is composed of the numerous high-density, controlled-release beads which are compressed into the form of tablet. Once the IPDAS® tablet is ingested it disintegrates & disperses the beads containing the drug in the stomach which subsequently passes into the duodenum & along the GI tract in the gradual & controlled manner independent of the feeding state. The Release of the active ingredient is controlled by the polymer system which is used to coat the beads or /and the micromatrix of the active /polymer ingredient formed in the spheronised /extruded multiparticulates. By virtue of the multiparticulate nature of the formulation the intestinal protection of IPDAS® technology is inherent, which ensures the wide dispersion of the irritant drug throughout the GI tract. The IPDAS® was initially designed as a part of the development process for the Elan Drug Technologies' proprietary naproxen formulation Naprelan®. Although the naproxen as the free

acid or the sodium salt has the pharmacokinetic characteristics that are consistent with once-daily dosing the gastrointestinal irritant & ulcerogenic potential associated with the large bolus dose of the naproxen precludes the safe use of an immediate-release form. For the prompt onset of analgesic activity as well as a prolonged phase of absorption, the desired pharmacodynamic activity of the once-daily dosage form of the naproxen requires rapidly available naproxen, to provide 24 hours anti-inflammatory/ analgesic activity. The objective was to develop the once-daily controlled release system with reduced gastric irritancy & with the fast onset of action. The objective was achieved in the Naprelan®; it has the proven onset of pain relief within the 30 min that lasts up to the 24 hours & has been shown to be well-tolerated. The advantages of the IPDAS® technology include the gastrointestinal protection for more locally irritant drugs (e.g., NSAIDs), the high-density multiparticulate formulation, advantages of the multiparticulate in the tablet form & fast onset if it is required.[39, 53, 59-60]

OROS® technology

The OROS delivery systems were adopted for the poorly water soluble drugs. The push-pull system is comprised of the bilayer or the trilayer tablet core consisting of the one push layer & one or more of the drug layers. The layer of drug contains the osmotic agents, suspending agent and the poorly soluble drugs. The push layer contains among the other things, an osmotic agent & the water swellable polymers. The tablet core is surrounded by the semipermeable membrane. Variety of the OROS® systems [ALZA Corp.] have been developed, Ditropan XL®, Concerta® & Procardia XL®, are the notable examples. Recently developed L-OROS® SOFTCAP™ delivery system combines the features of the controlled-release & bioavailability-enhanced delivery system to enhance the compliance & the therapeutic effect. The L-OROS™ technology was developed by the Alza to overcome the issue of solubility of drug. These formulations include the SEF [self-emulsifying liquid carrier formulations] that allow the drug to be more readily absorbed through the GI membrane & the blood stream. The self-emulsifying liquid carrier formulation in the L-OROS systems consists of the drugs in the non-aqueous liquid carriers formulated to give either the solution or the nanosuspension. As the drug in the solution is released in the gastrointestinal tract, it forms the very small droplets [< 100 nm] increasing the solubility of drugs, thereby enhancing the bioavailability. The drug nano particles are dispersed, as the drug in the nanosuspension is released & aggregation is prevented.[61-65]

Time multiple action delivery system [TMDS]

For the multiple ingredients within the single tablet in a programmed manner this system controls the release rates. Time multiple action delivery system technology allows for the release of more

than one active ingredient in the single tablet formulation to be released in the multiple profiles over the time.

Geomatrix™

In the form of the multi-layer tablet the new delivery device has recently been proposed for the constant drug release based on the Geomatrix® Technology. It consists of the hydrophilic matrix core, containing the active ingredient & 1 or 2 semi-permeable or the impermeable polymeric coatings [compressed barriers or films] applied on one or both the bases of the core. To achieve customized levels of controlled release of specific drugs the Geomatrix™ technology is applied & can achieve the simultaneous release of the 2 different drugs & different rates from the single tablet. The presence of the coatings modifies the swelling/ hydration rate of the core & reduces the surface area available for the release of drug. These partial coatings provide the modulation of the drug dissolution profile, that is, they reduce the release rate from the device & shift the typical time-dependent release rate towards the constant release of drug. To achieve the controlled release, the multilayered tablet constructed using the two basic components, the hydrophilic polymers, such as the HPMC [hydroxypropyl methyl cellulose] & the surface-controlling barriers. The active loaded core surface that is available for the release of drug when exposed to the fluid is controlled by the barrier layers. Using this novel technology, the SkyePharma has developed the Lodotra™ containing the rheumathoid arthritis drug. The Lodotra™ delivers the active pharmaceutical ingredient at the most suitable time of the day to treat the disease. The advantages of the Geomatrix™ technology are, to be manufactured by the readily available equipment, their ability to be easily incorporated into a production line, efficacy, reproducibility, controlled release of the poorly soluble drugs, the versatility of the release control mechanisms, bi-phasic drugs release, timed release of the drugs, at different rates release of two or more drugs, safety of use & pulsed release of drugs.[41, 59, 66-69]

OSDRC technology

The conventional dry-coated tablet [DC] method requires the core tablet preparation before & therefore the complicated procedure of the conventional dry-coated method increases the cost of manufacturing & the chance of the failure which may lead to the rise in the supply of core tablet. To solve this problem the OSDRC-technology [the one-step dry-coated tablet system, the OSDRC-system] was developed that employs the double-structure punch [the center punch & the outer punch] allowing for the DC tablets to be assembled in the single run. There are three steps in manufacturing process which consists of; the bottom layer [the first outer layer]the compression, the core compression & whole tablet compression which includes a upper layer & the side layer

[the second outer layer]. As the tablets are produced in the single step while the punches make one rotation on the turntable there is no longer any need for the separate stage to deliver the core.[69-72]

Diffutab®

The Diffutab technology enables the customized release profiles & region-specific delivery. The Diffutab technology incorporates the blend of the waxes & hydrophilic polymers that control the release of drug through the diffusion & erosion of the matrix tablet. For the high-dose products & drugs that require the sustained release or /& once-a-day dosing, the Diffutabs are particularly useful. The Eurand applied this technology to both the soluble & insoluble products. The Advantages of the Diffutabs are supporting sustained-release, once-a-day dosing & high drug loading, as the matrix tablets utilize the combination of the active drug & water soluble particles.[58, 73]

The Covera-HS

The Covera-HS is the first once a daily formulation of an anti-anginal /antihypertensive agent that uses the advanced tablet coating & the novel drug delivery system [NDDS] to mimic the body's typical 24 hours circadian variations in the heart rate & blood pressure. This unique delivery technology is called COER-24™ [Controlled-Onset-Extended-Release] was developed in the conjunction with the Alza Corp. The Covera-HS is the only controlled-release verapamil formulation that is currently approved with the indication for the management of both the angina pectoris [chest pain] & the hypertension [high blood pressure]. It is available in both the 180 mg & 240 mg tablets. For oral dosing at bedtime the Covera-HS is designed. The Peak concentration of the Covera-HS is delivered in the early waking hours, when the blood pressure & heart rate are rise at their highest rate. There is minimal drug delivery during the sleep when the blood pressure & the heart rate are at their lowest physiologic.[61]

CURRENT SITUATION AND FUTURE SCOPE

Since it requires the correct dose to reach the right site at the appropriate time the development of drug products by the pulsatile technology is very challenging. The novel pulsatile drug delivery system pays the more attention on the site & time specificity. In near future it is believed that the novel pulsatile drug delivery system will be explored in the management or treatment of some other chronic & terminal disease conditions like the diabetes where the dose is required at the different time intervals. Among these systems multiparticulate systems {For eg; the pellets} offer the various advantages over the single unit which includes the no risk of dose dumping, the flexibility of the blending units with the different release patterns as well as the short & reproducible GR time [gastric residence time] site & the time specific oral drug delivery have

recently been of the great interest in the pharmaceutical field to achieve the improved therapeutic efficacy. To prolong the gastric residence time, the GRDDS [Gastroretentive drug delivery system] is an approach thereby targeting the site specific drug release in the upper gastrointestinal tract. The bioadhesive drug delivery & the FDDS [floating drug delivery system] are widely used techniques for the gastro retention. For the formulation of floating drug delivery system the low density porous multiparticulate systems have been used by the researchers. The Sharma & Pawar have developed the multiparticulate floating pulsatile drug delivery systems by using the porous calcium silicate & the sodium alginate for the time & site specific drug release of the meloxicam.[74-75]

CONCLUSION

Currently, by far the most preferable route of drug delivery is the oral delivery of the drug due to the patient compliance, flexibility in its formulations & ease of administration. Generally the controlled & sustained release products provide the desired therapeutic effect but fall short of the diseases following the biological rhythms, circadian disorders such as the asthma, osteoarthritis, hypertension etc, which requires the chronopharmacotherapy. The pulsatile drug delivery system can effectively tackle this problem as it is modulated according to the body's circardian clock giving release of the drug after the specified time lag. The technologies to ensure the time controlled pulsatile release of the bioactive compounds have been developed for the last two decades. The significant progress has been made towards achieving the pulsatile drug delivery system that can effectively treat the diseases with the non-constant dosing therapies. Currently some of the pulsatile technologies are in the market & different pulsatile technologies are researched.

REFERENCES

1. Davis S.S & Illum L; Drug delivery systems for challenging molecules; Inj J Pharm 1998: 176: 1-8.
2. Youan BB; Chronopharmaceutic; gimmick or clinically relevant approach to drug delivery; J Control Res 2004: 98: 337-353
3. Maroni A, Zema L, Cerea M; Oral Pulsatile drug delivery systems Expt; Opinion Drug Del 2005: 2: 855-871
4. Pozzi F, Furlani P, Gazzaniga A, Davis SS, Wilding IR; The Time Clock System; A new oral dosage form for fast and complete release of drug after a predetermined lag time; J Control Release; 1994: 31: 99-108

5. Siegel RA and Pitt CG; A Strategy for oscillatory drug release; general scheme and simplified theory, J Control Rel, 1995:33: 173-188
6. Roy P, Shahiwala A; Multiparticulate formulation approach to pulsatile drug delivery; Current Perspectives, J Control Rel, 2009: 134: 74-80
7. Bhargavi R, Prabha SK, Tabasum MD; A comprehensive review on pulsatile drug delivery system; International Research Journal of Pharmacy. 3(3): 2012:106-108.
8. Parmar RD, Parikh RK, Vidyasagar G, Patel VD. Pulsatile drug delivery system: An Overview; International journal of pharmaceutical sciences and nanotechnology. 2(3): 2009: 605-614.
9. Rathod S; Colon Targeted Pulsatile Drug Delivery A Review. Pharmainfo net; 5(2): 2007:1-11.
10. Bi-Botti C. Youan; Chronopharmaceutics: gimmick or clinically relevant approach to drug delivery. J Controlled Release 2004: 98: 337– 353.
11. Nitin. D. Gajbhiye et al; Pulsatile drug delivery system. J Pharm Res 2013: (1):120-123.
12. Burnside B. A., Guo X., Fiske K., Couch R. A., Treacy D. J., Chang R. K., McGuinness, C.M., Rudnic, E.M.: US20036605300: (2003)
13. Vinupama et.al; pulsatile drug delivery system: A Review. Int bulletin of drug research; 1(1): 19-31.
14. Ketousetuo Kuotsu et.al; Drug delivery system based on chronobiology-A review; J Controlled Release 2010: 147: 314–325.
15. Gupta Anujet.al; Review on recent advances in pulsatile drug delivery systems: A vision for better future for treatment of diseases; Int Pharma Sci. 2012: 2 (2): 71-77.
16. V.N.L.Sirishaet.al; Pulsatile drug delivery system-a review; Int J Pharma Res Allied Sci 2012:1(3): 13-23.
17. Dubal Ashwini et al; Chronotherapy: a novel drug delivery system; Int J Res Ayurveda Pharm 2011: 2 (6): 1692-1700.
18. Sutar K.P et al; Use of chronotherapeutics in design of pulsatile delivery systems-A review; J Pharma Scientific Innovation 2012: 1(2): 50-55.
19. Meenu Rajput et al; Pulsatile drug delivery system: a review. Int J Res Pharm Biomedical Sci 2012: 3 (1): 118-124.
20. Ravikumar Reddy J. et al; Review on: pulsatile drug delivery systems; J Pharma. Sci Res2009:1(4): 109-115.

21. Chopra et al; Chronotropic systems: an emerging trend in drug delivery for pulsed release in chrono pharmacotherapy; Int J Pharma Clinical Res 2010: 2(1): 10-19.
22. Jigar D. Patel et.al; pulsatile drug delivery system: an "user-friendly" dosage form. J Pharma Res Health 2010: 2(2): 204-215.
23. Bussemer T. et al; A pulsatile drug delivery system based on rupturable coated hard gelatin capsules; J Controlled Release 2003: 93: 331-339.
24. Yui N, Okano T et al; Inflammation responsive degradation of cross linked hyaluronic acid gels; J Controlled Release 1992: 22: 105-116.
25. Sharma Ritika et al; Pulsatile drug delivery system: a review; Int Res J Pharm 2013: 3(7): 103-107.
26. Bae YH, Okano T, Hsu R, et al; Thermo-sensitive polymers as on–off switches for drug release; Makromol.Chem1987: 8: 481-485.
27. Patel Pavan Kumar et al; Pulsatile drug delivery system an overview; Asian J Pharma Sci Clinical Res 2011: 1(1): 44-51.
28. Hitesh Dalvadia, Jayvadan K P. et.al; Chronpharmaceutics pulsatile drug delivery system as current trend; Asian J Pharma Sci 2010: 5 (5): 207-230.
29. Srikanth M.V.et al; recent trends in pulsatile drug delivery systems -A review; Int J Drug Delivery 2010: 2: 200-212.
30. Patel Vipul P. et.al; Pulsatile drug delivery system for treatment of various inflammatory disorders: A review; Int J Drug Develop Res 2012: 4 (3): 67- 87.
31. Ritschel, Forusz WA; Chronopharmacology: a review of drugs studies, Methods Find. ExpClinPharmacol 16 (1): 1994: 57-75.
32. Belgamwar VS, Gaikwad MV, Patil GB, Surana S; Pulsatile drug delivery system; Asian J of Pharmaceutics 2(3): 2008: 141-145.
33. Sarawade A, Ratnaparkhi M.P., Chaudhri S; floating drug delivery system: An Overview; Int. J. Res. Dev.Pharm. L. Sci.; 2014: 3(5): 1106-1115.
34. Kumar GA, Bhat A, Lakshmi AP, Reddy K; An Overview of Stimuli-Induced Pulsatile Drug Delivery System; Int. J. of Pharm Tech Research 2010: 2: 3658-2375.
35. Moore JG, EnglertJr E; Circadian rhythm of gastric acid secretion in man, Nature 226: 1970: 1261–1262.
36. Cloud ML, Offen WW; Nizatidine versus placebo in gastroesophageal reflux disease, A6 week, multicenter, randomized, double blind comparison, Nizatidine; GastroesophagealRelux Disease Study Group. Dig Dis Sci 37: 1992: 865– 874.

37. Bogin RM, Ballard RD; The treatment of nocturnal asthma with pulsed release albuterol, Chest 1992:102:362-366
38. LiboY, James L, Josph A; Colonic-specific drug delivery: new approaches and Invitro/invivo evaluation, Int J Pharma 235: 2002: 1-15.
39. Shaji J, Chadawar V, Talwalkar P; Multiparticulate Drug Delivery System. The Indian Pharmacist; 2007:6:8-21.
40. Dey NS, Majumdar S, Rao MEB; Multiparticulate drug delivery systems for controlled release; Trop J Pharm Res. 2008:7:1067–75. Doi: 10.4314/tjpr.v7i3.14692. [Cross Ref]
41. SkyePharma. 2010. SkyePharma - Drug Delivery Specialists. Available from: www.skypharma.com
42. MiddleBrook Pharmaceuticals. Available from: www.victorypharma.com/
43. Steven AG; Biotherapeutics—from drug discovery to drug delivery, control release society Newsletter 2004: 21:3.
44. Conte U, Maggi L, Colombo P, La MA; Multi-layered hydrophilic matrices as constant release devices (Geomatrix® systems) J Contr Rel. 1993:26:39–47. Doi: 10.1016/0168-3659(93)90207-L. [Cross Ref]
45. Eurand S.P.A. Corporation; 2003; Minitabs in multiparticulate drug delivery. 75843477.
46. MacNeil ME, Rashid A, Stevens HN; Dispensing device; World Patent 1990; 9009168.
47. Fukui E, Miyamura N, Uemura K, Kobayashi M; Preparation of enteric coated timed-release press-coated tablets and evaluation of their function by in vitro and in vivo tests for colon targeting. Int J Pharm. 2000: 204:7–15. Doi: 10.1016/S0378-5173(00)00454-3. [PubMed] [Cross Ref]
48. Jose S, Dhanya K, Cinu TA, Litty J, Chacko AJ; Colon targeted drug delivery: Different approaches. J Young Pharmacist; 2009:1:13-9. Doi: 10.4103/0975-1483.51869. [Cross Ref]
49. Patel GC, Patel MM; developing a modified pulsincap system; Pharm Tech Europe 2009: 21.
50. Yu DG, Zhu LM, Branford-White CJ, Yang XL, Xiang LY; Three-dimensional printing in pharmaceutics: promises and problems. J Pharm Sci. 2008:97:3666–90. Doi: 10.1002/jps.21284. [PubMed] [Cross Ref]
51. Rowe CW, Katstra WE, Palazzolo RD, Giritlioglu B, Teung P, Cima MJ; Multimechanism oral dosage forms fabricated by three dimensional printing. J Control Release; 2000:66:11–7. Doi: 10.1016/S0168-3659(99)00224-2. [PubMed] [Cross Ref]

52. Katstra WE; Fabrication of complex oral drug delivery forms by Three Dimensional Printing, Massachusetts Institute of Technology 2001: 237-41.
53. Elan Drug Technologies. 2010. Oral Controlled Release; Available from: www.elandrugtechnologies.com/oral_controlled_release
54. Panoz DE. Geoghegan, Edward J, inventors. 1989 Sept. 15/ Controlled absorption pharmaceutical composition, US Patent 4863742.
55. Troy MH; Timing drug availability with therapeutic need; Speciality Pharma. 2006:2:1.
56. Steve E; Bioenhancement technologies improve absorption of insoluble drugs in oral dosage forms. Drug Deliv System; 2007:2:4.
57. Percel P, Vishnupad KS, Venkatesh GM, inventors. 2002 Dec. 31Timed sustained release systems for Propranolol.US 6500454.
58. Aptalis. 2011. Aptalis homepage. Available from: http://www.aptalispharma.com/
59. Verma RK, Garg S; Current status of drug delivery technologies and future directions; Pharmaceutical Technology; 2001;25:1–14.
60. Elan Corporation; 1997 Nov 4; Intestinal protective drug absorption system. US Patent 75111480.
61. Alza. Available from: www.alza.com
62. Rappar D; Oral extended release: Snapshots and benefits. Drug Delivery Technol. 2007:7:42.
63. Devesh AB, Pethe AM; Lipid technology-a promising drug delivery system for poorly water soluble drugs; Int J Pharm Res Devel; 2010:2:1-11.
64. Shram M, Romach M, Sellers E, Thipphawong J; Assessing the abuse potential of an oral osmotic-controlled extended release (OROS) hydromorphone compared to immediate release hydromorphone; J Pain. 2009:10:45–54. Doi: 10.1016/j.jpain.2009.01.188. [Cross Ref]
65. Zentner GM, Rork GS, Himmelstein KJ; The controlled porosity osmotic pump; J Control Release. 1985:1:269-82. doi: 10.1016/0168-3659(85)90003-3. [Cross Ref]
66. Conte U, Colombo P, Maggi L, La MA; Compressed barrier layers for constant drug release in swellable matrix tablets; STP Pharma Sci. 1994:4:107-13.
67. Conte U, Maggi L; Modulation of the dissolution profiles from Geomatrix multi-layer matrix tablets containing drugs of different solubility; Biomaterials. 1996:17:889–96. Doi: 10.1016/0142-9612(96)83284-4. [PubMed] [Cross Ref]

68. Conte U, La Manna A, Colombo P. 1992; Tablets with controlled-rate release of active substances. US Patent Application 07/926,380.
69. OSDrC. 2007. OSDrC Technologies. Available from: www.osdrc.com
70. Ozeki Y, Danjo K; Development of one-step dry-coated tablet system (OSDRC-System) and the comparison of its compression characteristics with those of conventional dry-coated tablets; J Pharm Sci Technol 2004:64:59-66.
71. Yuichi O, Masaki A, Yukinao W, Kazumi D; Evaluation of novel one-step dry-coated tablets as a platform for delayed-release tablets; J Cont Rele. 2004:95:51-60. Doi: 10.1016 /j.jconrel. 2003:10.028. [PubMed] [Cross Ref]
72. Ozeki Y, Watanabe Y, Okamoto H, Danjo K; Development of dividable one-step dry-coated tablets (dividable-OSDRC) and their evaluation as a new platform for controlled drug release. Pharm Res. 2004:21: 1177–83. Doi: 10.1023/B:PHAM.0000033004.88953.bc. [PubMed] [Cross Ref]
73. Bussemer T, Otto I; Bodmeier R. Pulsatile drug-delivery systems; Crit Rev Ther Drug Carrier Syst. 2001:18:433-58. [PubMed]
74. Tajane S, R, Kholwal B.B, Suryawanshi S.S, & Tarkase K.N; Current Trends in Pulsatile Drug Delivery System; International Journal of Pharmaceutical Science and Research, 2012: 3(2): 358-366
75. Sharma S & Pawar A; Low Density Multiparticulate System for Pulsatile release of meloxicam; Int J Pharm; 2006: 313:150-158.