IJPSR (2012), Vol. 3, Issue 02 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 19 October, 2011; received in revised form 01 December, 2011; accepted 13 January, 2012

CURRENT TRENDS IN PULSATILE DRUG DELIVERY SYSTEMS

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Keywords:
Pulsatile drug delivery system,
single unit system,
multiple unit system,
pulsincap,
capsular system

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ABSTRACT

The purpose for this review on pulsatile drug delivery systems (PDDS) is to compile the recent literatures with special focus on the different types and approaches involved in the development of the formulation. Pulsatile drug delivery system is the most interesting time and site-specific system. This system is designed for chronopharmacotherapy. Thus, to mimic the function of living systems and in view of emerging chronotherapeutic approaches, pulsatile delivery, which is meant to release a drug following programmed lag phase, has increasing interest in the recent years. Diseases wherein PDDS are promising include asthma, peptic ulcer, cardiovascular diseases, arthritis, and attention deficit syndrome in children, cancer, diabetes, and hypercholesterolemia. Pulsatile drug delivery system divided into 2 types' preplanned systems and stimulus induced system, preplanned systems based on osmosis, rupturable layers, and erodible barrier coatings. Stimuli induced system based on electrical, temperature and chemically induced systems. This review also summarizes some current PDDS already available in the market. These systems are useful to several problems encountered during the development of a pharmaceutical dosage form.

INTRODUCTION: Controlled drug delivery systems have acquired a centre stage in the arena of pharmaceutical R&D business. Such systems offer temporal and/or spatial control over the release of drug and grant a new lease on life to a drug molecule in terms of patentability. The controlled drug delivery system offers many advantages, such as nearly constant drug level at the site of action, prevention of peak-valley fluctuations, reduction in dose of drug, reduced dosage frequency, avoidance of side effects, and improved patient compliance [1].

Pulsatile drug delivery systems (PDDS) are gaining a lot of interest and attention these days. These systems have a peculiar mechanism of delivering the drug rapidly and completely after a "lag time," i.e., a period of "no drug release." Though most delivery systems are designed for constant drug release over a prolonged period of time, pulsatile delivery systems are characterized by a programmed drug release, as constant blood levels of a drug may not always be desirable (**Fig. 1**).

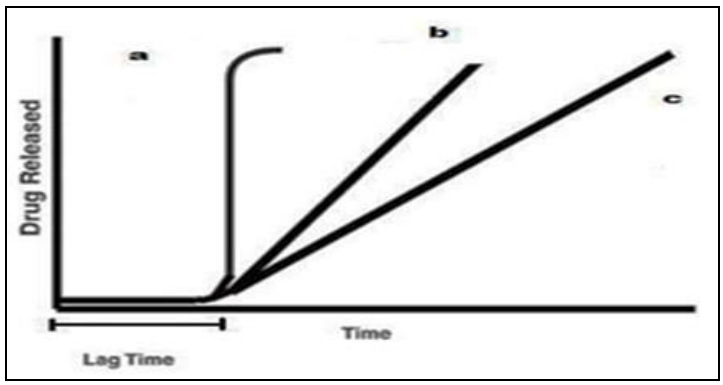

FIG. 1: DRUG RELEASE PATTERNS: - a) PULSATILE b) And c) OTHER CONVENTIONAL EXTENDED RELEASE DOSAGE FORMS

Pulsatile systems are designed in a manner that the drug is available at the site of action at the right time in the right amount. These systems are beneficial for drugs having high first-pass effect; drugs administered for diseases that follow chronopharmacological behaviour; drugs having specific absorption site in GIT, targeting to colon; and cases where night time dosing is required [2].

The focus of the present review is primarily on the pulsatile drug delivery methodologies and the upcoming technologies, which are being exploited on a new technique development [2].

Diseases targeted for Pulsatile Drug Delivery System: Diseases presently targeted for chronopharmaceutical formulations are those for which there are enough scientific backgrounds to justify PDDS- compared to the conventional drug administration approach [3]. They include: hypercholesterolemia, asthma, cancer, duodenal ulcer, arthritis, diabetes, neurological disorders, cardiovascular diseases (e.g., hypertension and acute myocardial infarction) and colonic delivery. The rationale for chronotherapy/pulsatile release for each of these diseases will be briefly reviewed below [6].

- **Hypercholesterolemia:** Diverse directions of circadian changes in lipid fractions in patients and normal subjects may contribute to alteration in the rhythmicity of other metabolisms and in the blood coagulation system, thus leading to various complications [7]. A circadian rhythm occurs during hepatic cholesterol synthesis. Therefore, cholesterol synthesis is generally higher during the night than during daylight, the maximal production occurs early in the morning, i.e., 12 h after the last meal [8, 9].

- **Asthma:** The chronotherapy of asthma has been extensively studied. The role of circadian rhythms in the pathogenesis and treatment of asthma indicates that airway resistance increases progressively at night in asthmatic patients [10]. Circadian changes are seen in normal lung function, which reaches a low point in the early morning hours. As broncho constriction and exacerbation of symptoms vary in a circadian fashion, asthma is well suited for chronotherapy. Chronotherapies have been studied for asthma with oral corticosteroids, theophylline, and β2-agonists [12].

- **Cancer:** Human and animal studies suggest that chemotherapy may be more effective and less toxic if cancer drugs are administered at carefully selected times that take advantage of tumour cell cycles while less toxic to normal tissue. The blood flow to tumours was threefold greater during each daily activity phase of the circadian cycle than during the daily rest phase. The chronotherapy concept offers further promise for improving current cancer-treatment options, as well as for optimizing the development of new anticancer or supportive agents [12, 13].

- **Duodenal ulcer:** Many of the functions of the gastrointestinal tract are subject to circadian rhythms: gastric acid secretion is highest at night, while gastric and small bowel motility and gastric emptying are all slower at night. During night time, when gastric motility and emptying are slower, drug disintegration, dissolution, and absorption may be slower. In peptic ulcer patients, gastric acid secretion is highest during the night. Suppression of nocturnal acid is an important factor in duodenal ulcer healing. Therefore, for active duodenal ulcer, once daily at bedtime is the recommended dosage regimen for an H2 antagonist [13, 14].

- **Arthritis:** The chronobiology, chronopharmacology and chronotherapeutics of pain have been extensively reviewed. For instance, there is a circadian rhythm in the plasma concentration of C - reactive protein and interleukin-6 of patients with rheumatoid arthritis. Patients with osteoarthritis tend to have less pain in the morning and more at night; while those with rheumatoid arthritis, have pain that usually peaks in the morning and decreases throughout the day. Chronotherapy for all forms of arthritis using NSAIDs such as Ibuprofen should be timed to ensure that the highest blood levels of the drug coincide with peak pain [15, 16].

- **Diabetes:** The circadian variations of glucose and insulin in diabetes have been extensively studied and their clinical importances in case of insulin substitution in type I diabetes have been previously

discussed. The goal of insulin therapy is to mimic the normal physiologic pattern of endogenous insulin secretion in healthy individuals, with continuous basal secretion as well as meal-stimulated secretion [18, 19].

- **Neurological disorders:** As an integrative discipline in physiology and medical research, chronobiology renders the discovery of new regulation processes regarding the central mechanisms of epilepsy. Chronophysiology investigations considered at a rhythmometric level of resolution suggest several heuristic perspectives regarding (i), the central pathophysiology of epilepsy and (ii) the behavioural classification of convulsive events [20].

- **Cardiovascular diseases:** Several functions such as, Blood pressure (BP), heart rate, stroke volume, cardiac output, blood flow of the cardiovascular system is subject to circadian rhythms. For instance, capillary resistance and vascular reactivity are higher in the morning and decrease later in the day. Platelet aggregability is increased and fibrinolytic activity is decreased in the morning, leading to a state of relative hypercoagulability of the blood [21]. It was postulated that modification of these circadian triggers by pharmacologic agents may lead to the prevention of adverse cardiac events. BP is at its lowest during the sleeping period and rises steeply during the early morning period. Most patients with essential hypertension have a similar circadian rhythm of BP as do normotensive persons, although hypertensive patients have an upward shift in the profile [22].

- **Colonic delivery:** The colon is also seen as the preferred absorption site for oral administration of protein and peptide drugs, because of the relatively low proteolytic enzyme activities in the colon. A colon-specific drug delivery system should prevent drug release in the stomach and small intestine, and affect an abrupt onset of drug release upon entry into the colon. Time dependent delivery has also been proposed as a means of targeting the colon. Time-dependent systems release their drug load after a pre-programmed time delay. To attain colonic release, the lag time should equate to the time taken for the system to reach the colon. This time is difficult to predict in advance, although a time lag of five hours is usually considered sufficient, given that small intestinal transit time is reported to be relatively constant at three to four hours [23].

All of these conditions demand a time-programmed therapeutic scheme releasing the correct amount of dose of the drug at the appropriate time. This requirement is usually fulfilled by PDDS [24].

Methodologies for PDDS:

A. Pre Planned Systems:

a. Single unit systems:

- **Capsular system:** Different single-unit capsular pulsatile drug delivery systems have been developed. A general architecture of such systems consists of an insoluble capsule body housing a drug and a plug. The plug is removed after a predetermined lag time owing to swelling, erosion, or dissolution. The Pulsincap® system (Scherer DDS, Ltd) is an example of such a system that is made up of a water-insoluble capsule body filled with drug formulation (**Fig. 2**). The body is closed at the open end with a swellable hydrogel plug. Upon contact with dissolution medium or gastro-intestinal fluids, the plug swells, pushing itself out of the capsule after a lag time. This is followed by a rapid drug release. The lag time can be controlled by manipulating the dimension and the position of the plug. For water-insoluble drugs, a rapid release can be ensured by inclusion of effervescent agents or disintegrants.

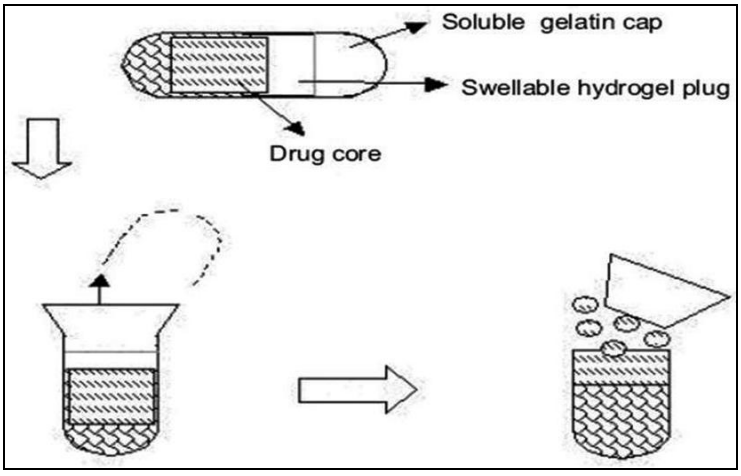

FIG. 2: DESIGN OF PULSINCAP® SYSTEM

The plug material consists of insoluble but permeable and swellable polymers (e.g. polymethacrylates), erodible compressed polymers (e.g. hydroxypropylmethyl cellulose, polyvinyl alcohol, polyethylene oxide), congealed melted polymers (e.g. saturated polyglycolated glycerides, glyceryl monooleate), and enzymatically controlled erodible polymer (e.g., pectin). These formulations were well tolerated in animals and healthy volunteers, and there were no reports of gastro-intestinal irritation. However, there was a potential problem of variable gastric residence time, which was overcome by enteric coating the system to allow its dissolution only in the higher pH region of small intestine [27, 29].

- **A System Based on Osmosis:** The Port® System (Port Systems, LLC) consists of a gelatin capsule coated with a semi permeable membrane (e.g. cellulose acetate) housing an insoluble plug (e.g. lipidic) and an osmotically active agent along with the drug formulation (**Fig. 3**). When in contact with the aqueous medium, water diffuses across the semi permeable membrane, resulting in increased inner pressure that ejects the plug after a lag time [32]. The lag time is controlled by coating thickness. The system showed good correlation in lag times of *in-vitro* and *in-vivo* experiments in humans. The system was proposed to deliver methylphenidate for the treatment of attention deficit hyperactivity disorder (ADHD) in school-age children [33].

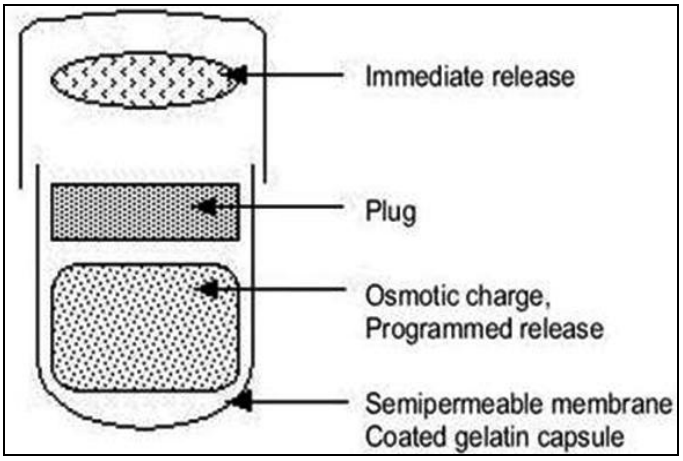

FIG. 3: DRUG RELEASE FROM PORT® SYSTEM

- **A System Based on Expandable Orifice:** To deliver the drug in liquid form, an osmotically driven capsular system was developed in which the liquid drug is absorbed into highly porous particles, which release the drug through an orifice of a semi permeable capsule supported by an expanding osmotic layer after the barrier layer is dissolved. The capsular system delivers drug by the capsule's osmotic infusion of moisture from the body. The capsule wall is made up of an elastic material and possesses an orifice. As the osmosis proceeds, the pressure within the capsule rises, causing the wall to stretch.

  The orifice is small enough so that when the elastic wall relaxes, the flow of the drug through the orifice essentially stops, but when the elastic wall is distended beyond threshold value, the orifice expands sufficiently to allow drug release at a required rate. Elastomers, such as styrene-butadiene copolymer have been suggested. Pulsatile release was achieved after lag times of 1 to 10 hours, depending on the thickness of the barrier layer and that of semi permeable membrane, and a capsule designed for implantation can deliver drug intermittently at intervals of 6 hours for 2 days [35].

- **Delivery by a Series of Stops:** This system is described for implantable capsules. The capsule contains a drug and a water-absorptive osmotic engine that are 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. The number of stops and the longitudinal placements of the stops along the length of the capsule dictate the number and frequency of the pulses, and the configuration of the partition controls the pulse intensity. This system was used to deliver porcine somatotropin [36].

- **Delivery by Solubility Modulation:** Such systems contain a solubility modulator for pulsed delivery of variety of drugs. The system was especially developed for delivery of salbutamol sulphate. The compositions contain the drug (salbutamol sulphate) and a modulating agent (sodium chloride, NaCl). The amount of NaCl was such that it was less than the amount needed to maintain saturation in

a fluid that enters the osmotic device. The pulsed delivery is based on drug solubility. The solubility of the drug is function of the modulator concentration, while the modulator's solubility is largely independent of drug concentration. The modulating agent can be a solid organic acid, inorganic salt, or organic salt. In order to control zero-order release period and commencement of pulsed release, ratio of drug/modulator can be varied. After the period of zero-order release, the drug is delivered as one large pulse [38]. A similar system is described for delivery of terbutaline and oxprenolol.

However, in general, the large-scale manufacturing of these systems is complicated and calls for special equipments and several manufacturing steps [40].

b. Multiple Unit Systems:

- **Pulsatile System with Erodible or Soluble Barrier Coatings:** Most of the pulsatile drug delivery systems are reservoir devices coated with a barrier layer (**Fig. 4**). This barrier erodes or dissolves after a specific lag period, and the drug is subsequently released rapidly. The lag time depends on the thickness of the coating layer. The Time Clock® system (West Pharmaceutical Services Drug Delivery & Clinical Research Centre) consists of a solid dosage form coated with lipidic barriers containing carnuba wax and bees' wax along with surfactants, such as polyoxyethylene sorbitan monooleate.

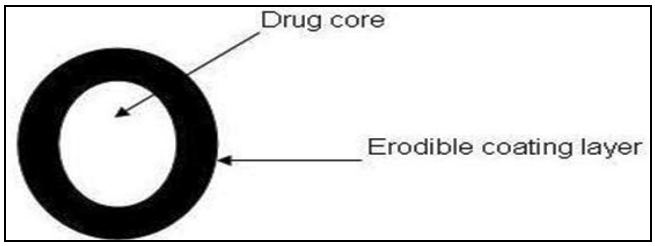

FIG. 4: DELIVERY SYSTEM WITH ERODIBLE COATING LAYER

This coat erodes or emulsifies in the aqueous environment in a time proportional to the thickness of the film, and the core is then available for dispersion. In a study with human volunteers, it was shown that the lag time was independent of gastric residence time, and the hydrophobic film redispersion did not appear to be influenced by the presence of intestinal enzymes or mechanical action of stomach or gastro-intestinal pH. The lag time increased with increasing coating thickness. Such systems are better suited for water-soluble drugs. The major advantage of this system is its ease of manufacturing without any need of special equipment.

However, such lipid-based systems may have high *in-vivo* variability (e.g., food effects). The possible problems of erosion-controlled systems include a premature drug release when the penetrating water dissolves the drug, which diffuses out through the barrier layers, and sustained release after the lag phase when the barrier layer is not eroded or dissolved completely, thereby retarding the drug release [30, 31].

The Chronotropic® system consists of a drug-containing core coated by hydrophilic swellable hydroxypropylmethyl cellulose (HPMC), which is responsible for a lag phase in the onset of release. In addition, through the application of an outer gastric-resistant enteric film, the variability in gastric emptying time can be overcome, and a colon-specific release can be obtained, relying on the relative reproducibility of small intestinal transit time. The lag time is controlled by the thickness and the viscosity grades of HPMC.

The cores containing Antipyrine as the model drug were prepared by tabletting and retarding, and enteric coats were applied in a fluidized bed coater. The *in-vitro* release curves displayed a lag phase preceding drug release, and the *in-vivo* pharmacokinetic data showed a lag time prior to presence of detectable amounts of drug in saliva. Both *in-vitro* and *in-vivo* lag times correlate well with the applied amount of the hydrophilic retarding polymer. The system is suitable for both tablets and capsules [34].

- **Pulsatile System with Rupturable Layers/ Membranes:** Similar to single-unit system, the rupturing effect is achieved by coating the individual units with effervescent or swelling agents. Bai *et al.* invented a pulsatile drug delivery system comprising of a plurality of particles that are divided into several individual delivery units,

each having its own distinct composition. Drug delivery was controlled by the rupture of the membrane (**Fig. 5**). The timing of release was controlled by the thickness of coating and the amount of water-soluble polymer to achieve the pulsed release. The individual particles had the same composition of internal core, but the thickness of the external coating layer varied [39].

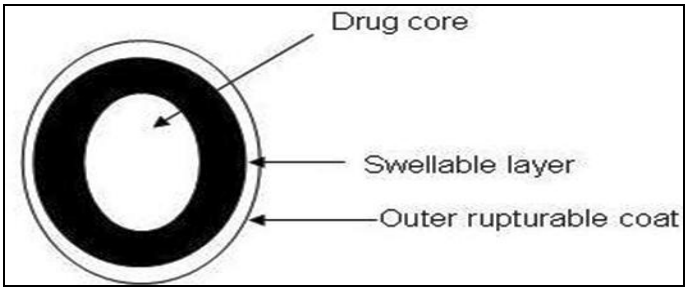

FIG. 5: DELIVERY SYSTEM WITH RUPTURABLE LAYERS

B. Stimuli Induced Pulsatile Systems

I. Temperature induced system
II. Chemically induced System
III. Externally induced System

i. Temperature Induced System: 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 200C and 300C by using reversible swelling properties of copolymers of N-isopropylacrylamide and butyrylacrylamide [40].

ii. 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 enzyme or protein. One prominent application of this technology has been development of a system that can autonomously release insulin in response to elevated blood glucose levels. Several existing strategies that may be feasible for glucose-responsive drug delivery are discussed below: pH-dependent systems for Glucose stimulated drug delivery are based on the reaction that glucose oxidase catalyses oxidation of glucose to gluconic acid. This reaction can be used to drive the swelling of pH-dependent membrane. A dual membrane system was formed. In the first membrane, glucose oxidase was immobilized on cross linked polyacrylamide and this was referred to as glucose sensing membrane. Co-polymer membrane composed of N, N- diethylaminoethyl methacrylate and 2-hydroxypropyl methacrylate (DEA-HPMA) formed the barrier membrane and worked as an interface between insulin reservoir and sensing membrane [56].

In pH sensitive system there are two components one is of immediate release type and other one is pulsed release which releases the drug in response to change in pH. In case of pH dependent system advantage has been taken of the fact that there exists different pH environment at different parts of the gastrointestinal tract. By selecting the pH dependent polymers drug release at specific location can be obtained. Examples of pH dependent polymers include cellulose acetate phthalate, polyacrylates, and sodium carboxymethyl cellulose. These polymers are used as enteric coating materials so as to provide release of drug in the small intestine.

Yang *et al*., developed pH-dependent delivery system of nitrendipine in which they have mixed three kinds of pH dependent microspheres made up of acrylic resins Eudragit E-100, Hydroxypropyl-methylcellulose phthalate and Hydroxypropyl-methylcellulose acetate succinate as pH dependent polymers. In one of the study carried out by Mastiholimath *et al.*, attempt was made to deliver theophylline into colon by taking the advantage of the fact that colon has a lower pH value (6.8) than that of the small intestine (7.0-7.8). So, by using the mixture of the polymers, i.e. Eudragit L and Eudragit S in proper proportion, pH dependent release in the colon was obtained.

iii. Externally Induced System: 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.

1. **Magnetically stimulated:** Saslawski *et al*., 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 [60].

2. **Ultrasonically stimulated:** Ultrasound is mostly used as an enhancer for the improvement of drug permeation through biological barriers, such as skin, lungs, intestinal wall and blood vessels. There are several reports describing the effect of ultrasound on controlled drug delivery. Kost *et al.,* described an ultrasound-enhanced polymer degradation system. During polymer degradation incorporated drug molecules were released by repeated ultrasonic exposure. As degradation of biodegradable matrix was enhanced by ultrasonic exposure, the rate of drug release also increased. Thus, pulsed drug delivery was achieved by the on-off application of ultrasound. Miyazaki *et al*., used ultrasound to achieve up to a 27-fold increase in the release of 5-fluorouracil from an ethylene and vinyl acetate (EVAc) matrix. Increasing the strength of the ultrasound resulted in a proportional increase in the amount of 5-fluorouracil released.

3. **Photo stimulated:** The interaction between light and material can be used to modulate drug delivery. This can be accomplished by combining a material that absorbs light at a desired wavelength and a material that uses energy from the absorbed light to modulate drug delivery.

4. **Electrically stimulated:** An electric field as an external stimulus has advantages such as availability of equipment, which allows precise control with regards to the magnitude of the current, duration of electric pulses, interval between pulses etc. Electrically responsive delivery systems are prepared from polyelectrolytes and are thus pH- responsive as well as electro responsive. Under the influence of electric field, electro responsive hydrogels generally deswell, swell or erode. This rapid drug release was attributed to the electrostatic force, squeezing effect, and electro-osmosis of the gel. Complete on-off drug release was achieved, as no drug release was apparent without the application of electric current [58].

Future Trends in Pulsatile Drug Delivery System: The development of drug products by pulsatile technology is very challenging since it requires the correct dose to reach the right site at the appropriate time. However, the novel PDDS pays more attention on site and time-specificity. It is believed that in the near future novel PDDS will be explored in the treatment or management of some other chronic and terminal disease conditions like diabetes where dose is required at different time intervals. Among these systems, multi-particulate systems (e.g. pellets) offer various advantages over single unit which include no risk of dose dumping, flexibility of blending units with different release patterns, as well as short and reproducible gastric residence time. Some latest pulsatile technologies are shown in **table 1**.

TABLE 1: MARKETED TECHNOLOGIES OF PULSATILE DRUG DELIVERY

Technology	Mechanism	Proprietary name and dosage form	API	Disease	References
OROS®	Osmotic Mechanism	Covera-HS®; XL	Verapamil HCL	Hypertension	60
CODAS®	Multiparticular pH dependent system	Verelan® PM; XL	Verapamil HCL	Hypertension	61
DIFFUCAPS®	Multiparticulate System	Innopran®; XL	Verapamil HCL, Propranolol HCL	Hypertension	62
Three dimen-sional printing®	Externally regulated system	TheirForm®	Diclofenac Na	Inflammation	63
PulsincapTM	Rupturable system	PulsincapTM	Dofetilide	Hypertension	64
Pulsys®	Timed-controlled System	Pulsys®	Amoxicillin	pharyngitis/tonsillitis	65

CONCLUSION: Universally sustained and controlled release products provide a desired therapeutic effect, but fall for diseases following biological rhythms. It can be concluded that pulsatile drug delivery systems offer a solution for delivery of drugs exhibiting chronopharmacological behaviour, extensive first-pass metabolism, necessity of night-time dosing, or absorption window in GIT. The time controlling system character of these systems is useful for treatment of patients, due to their resulting efficiency and lack of undesirable adverse effects to the whole body. Delivering drug at the right time, right place, and in right amounts, holds good promises of benefit to the patients.

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