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ADVANCED DRUG DELIVERY IN DESIGNING OF BIOLOGICAL RHYTHM THROUGH PULSATILE DRUG DELIVERY SYSTEM: CURRENT STATE OF ART

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ABSTRACT

Pulsatile drug delivery systems are gaining a lot of interest as they deliver the drug at the right place at the right time in the right amount, thus providing a spatial, temporal and smart delivery in increasing patient compliance in designing according to the biological rhythm of the body. Here drug delivery is facilitated according to disease rhythm. The principle rationale for the use of pulsatile release of the drugs is where a constant drug release is not desired. A pulse has to be designed in such a way that a complete and rapid drug release is achieved after the lag time. Various systems like capsular systems, osmotic systems, single and multiple-unit systems based on the use of soluble or erodible polymer coating membranes have been dealt with in the article. It summarizes the latest developments in formulating parameters in release profiles of systems. These systems are beneficial for the drugs having Chrono pharmacological behavior such as a drug used in the treatment of bronchial asthma, myocardial infarction and ankylosing spondylitis like inflammatory disorders. Current review article discussed the reasons for the development of pulsatile drug delivery system in designing of circadian rhythm, types of the disease in which pulsatile release is required, classification, advantages, limitation, and future aspects of pulsatile drug delivery system.

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INTRODUCTION

Nowadays, the emphasis of pharmaceutical researchers is turned towards the development of more efficacious drug delivery systems with the already existing molecule. Modified release dosage forms have great importance in this regard. Such systems control the release pattern of the drug, either with constant or with predetermined release rates. It can be achieved by pulsatile drug delivery system which is defined as the rapid and transient release of a certain amount of molecules within a short time period immediately after a predetermined rate. A pulse has to be generated in such a way that a complete and rapid drug release is achieved after the lag time so as to match circadian rhythms with the release of drugs [1].

This can be classified according to the pulse-regulation of drug release into three main classes, time-controlled pulsatile release (single or multiple unit systems), internal stimuli- induced pulsatile release and external stimuli-induced pulsatile release systems.

CIRCADIAN RHYTHM

Circadian rhythms are self-sustaining, endogenous oscillations that occur with a periodicity of about 24 hours. These rhythms allow the organism to anticipate and prepare for precise and regular environmental changes. There are clear patterns of core body temperature, brain wave activity, hormone production, and other biological activities linked to this cycle. Some people function best in the morning while others have their peak in the noon or evening. If our normal rhythm is disrupted we tend to become anxious e.g. many people have difficulty in adjusting to swing-shift work schedules [2].

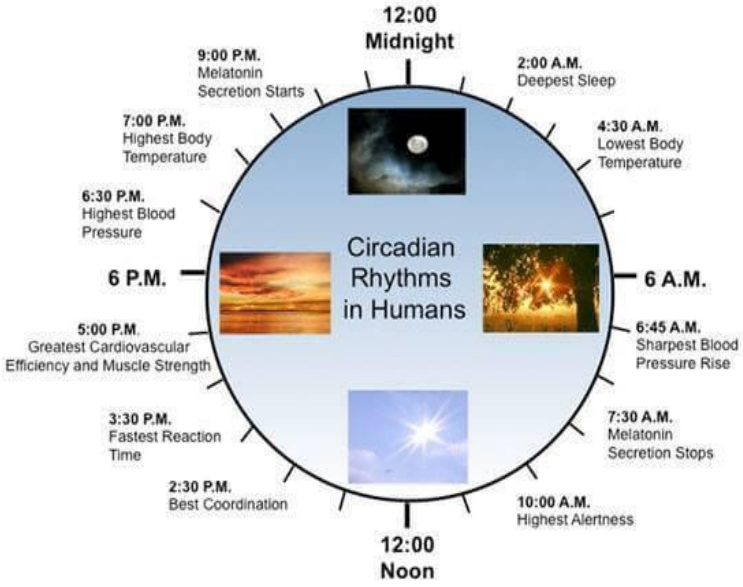

Figure 1: Circadian rhythms which are endogenous oscillations occurring with a periodicity of about 24hours and showing the clear patterns of core body temperature, hormone production, and other biological activities.

NEED OF PULSATILE DRUG DELIVERY

Below are the basic advantages of pulsatile drug delivery over conventional drug delivery.

First pass metabolism:

Some drugs, such as salicylamide and beta blockers, undergo extensive first-pass metabolism. So, in order to avoid first-pass metabolism, it is advisable to use pulsatile drug delivery systems over conventional or sustained drug delivery dosage form. [3]

Biological tolerance:

Continuous release drug plasma profiles are often accompanied by a decline in the pharmacotherapeutic effect of the drug, e.g., biological tolerance of transdermal nitro-glycerine. [4]

Special Chrono pharmacological needs:

Circadian rhythms in certain physiological functions are well established. It has been recognized that many symptoms and onset of disease occur during specific time periods of the 24-hour day. E.g. asthma and angina pectoris attacks, arthritis is most frequently in the morning hours [5].

ADVANTAGES

1) Predictable, reproducible also short gastric residence time
2) Not only Less inter- but also intra-subject variability
3) Improved bioavailability
4) Reduced adverse effects and improved tolerability
5) No risk of dose dumping
6) Flexibility in design
7) Improve stability [6]

DISADVANTAGES

1) Lack of Formulation reproducibility and efficacy
2) Large number of process variables
3) Multiple manufacturing steps
4) Production of high cost
5) The need for advanced technology
6) Trained/skilled person needed for Production [7]

CHRONOLOGICAL BEHAVIOUR TOWARDS PULSATILE DRUG DELIVERY

Chronotherapeutic

Chronotherapeutic is a discipline concerned with the delivery of drugs according to inherent activities of a disease over a certain period of time. The tradition of prescribing medication at evenly spaced time intervals throughout the day, in an attempt to maintain constant drug levels throughout a 24 hr period, may be indicating that some medications may work better if their administration is coordinated with day-night patterns and biological rhythms. [8-9]

Chronopharmacokinetics

Chronopharmacokinetic involves the study of temporal changes in drug absorption, distribution, metabolism, and excretion. Pharmacokinetic parameters, which are conventionally considered to be constant in time, are influenced by different physiological functions displaying circadian rhythm. Circadian changes in gastric acid secretion, gastrointestinal motility, gastrointestinal blood flow, drug-protein binding, liver enzyme activity, renal blood flow, and urinary pH can play role in time-dependent variation of drug plasma concentrations. Co-ordination of biological rhythms and medical treatment is called chronotherapy. [10]

TECHNOLOGIES INDUCED IN PULSATILE DRUG DELIVERY

Capsular systems

Single-unit systems are mostly developed in capsule form. The lag time is controlled by a plug, which gets pushed away by swelling or erosion, and the drug is released as a "Pulse" from the insoluble capsule body. [11]

Osmosis based system

This system contains a drug and a water-absorptive osmotic agent 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. Osmotic delivery capsules ("osmotic pumps") function by virtue of walls which selectively pass water into the capsule reservoir. Absorption of water by the capsule through these walls is driven by a water-attracting agent in the capsule interior which creates osmotic pressure across the capsule wall as represented in Fig.2[12-13].

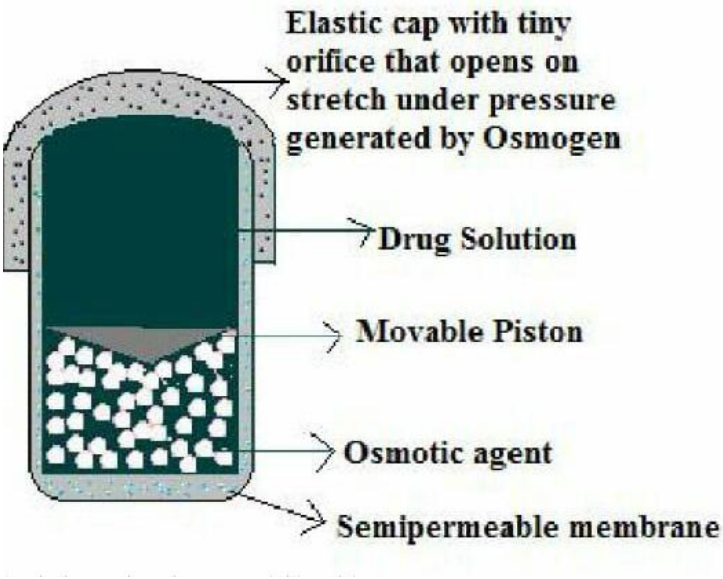

Figure 2: Osmotic system consisting of drug solution can obstruct the movement of the partition but are overcome in successive as osmotic pressure rises above a threshold level.

Drug delivery system with eroding or soluble barrier coating

These systems are based upon a drug reservoir surrounded with a soluble barrier layer that dissolves with time, and the drug releases at once after this lag time. The chronotropic system consists of a core containing drug reservoir coated by a hydrophilic polymer HPMC. An additional enteric-coated film is given outside this layer to overcome intra-subject variability in gastric emptying rates. The lag time and the onset of action are controlled by the thickness and the viscosity grade of HPMC. [14]

Drug delivery system with rupturable layers or membranes

These systems are based upon a reservoir system coated with a rupturable membrane. The outer membrane ruptures due to the pressure developed by effervescent agents or swelling agents. A pulsatile system with a rupturable coating on drug present in hard gelatin capsules. These capsules were first coated with a swelling layer and then with an insoluble but water-permeable outer coating. These coated capsules, when immersed in the release media, could take up the media at a constant rate up to a point when the outer coating would rupture because of the pressure caused by the swelling lay.[14-15].

Time clock systems

The time clock system consists of a solid dosage form coated with lipid barriers containing carnauba wax and beeswax along with surfactants, such as polyoxyethylene sorbitan monooleate. 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. [16]

Chronotropic systems

The chronotropic system consists of a drug containing core coated by hydrophilic swellable hydroxyl propyl methyl cellulose (HPMC), which is responsible u a lag phase in the onset of drug release. The time lag is controlled by the thickness and the viscosity grades of HPMC used in coating the drug core. The system is suitable for both tablets and capsule formulations. [16-17].

PULSATILE DELIVERY BY CHANGE IN MEMBRANE PERMEABILITY:

Numerous pharmaceutical forms with a delayed release for oral administration are available. As already mentioned, the release of the drug must be controlled according to therapeutical purpose and the pharmacological properties of the active ingredient. In consequence, it is not always desirable the blood levels be constant. On the contrary, in order to avoid any habituation and in order to limit the side effects provoked by the active ingredient, it would be advantageous for the plasmatic rate to follow the metabolic rhythm and the specific needs of the patient during certain periods. [18].

CHEMICAL STIMULI INDUCED PULSATILE SYSTEMS

a) Glucose-responsive insulin release devices -In the case of diabetes mellitus there is a rhythmic increase in the levels of glucose in the body requiring injection of the insulin at a proper time. Several systems have been developed which are able to respond to changes in glucose concentration. One such system includes pH-sensitive hydrogel containing glucose oxidase immobilized in the hydrogel. When glucose concentration in the blood increases glucose oxidase converts glucose into gluconic acid which changes the pH of the system. This pH change induces swelling of the polymer which results in insulin release. Insulin by virtue of its action reduces blood glucose level and consequently, gluconic acid level also gets decreased and the system turns to the deswelling mode thereby decreasing the insulin release. [19]

(b) Inflammation-induced pulsatile release device-On receiving any physical or chemical stress, such as injury, fracture etc. Inflammation takes place at the injured sites.

During inflammation, hydroxyl radicals are produced from these inflammation- responsive cells focused on the inflammatory-induced hydroxyl radicals and designed drug delivery systems, which responded to the hydroxyl radicals and degraded in a limited manner. They used hyaluronic acid (HA) which is specifically degraded by the hyaluronidase or free radicals. Degradation of HA via the hyaluronidase is very low in a normal state of health. Degradation via hydroxyl radicals, however, is usually dominant and rapid when HA is injected at inflammatory sites. Thus, it is possible to treat patients with inflammatory diseases like rheumatoid arthritis; using anti-inflammatory drug incorporated HA gels as new implantable drug delivery systems [20]

(c) Drug release from intelligent gels responding to antibody concentration There are numerous kinds of bioactive compounds which exist in the body. Recently, novel gels were developed which responded to the change in concentration of bioactive compounds to alter their swelling/reselling characteristics.

LOW-DENSITY FLOATING MULTIPARTICULATE PULSATILE SYSTEM

Conventional multiparticulate pulsatile release dosage forms mentioned above are having a longer residence time in the gastrointestinal tract and due to highly variable nature of the gastric emptying process, may result in vivo variability and bioavailability problems. In contrary, low density floating multiparticulate pulsatile dosage forms reside in the stomach only and not affected by the variability of pH, local environment or gastric emptying rate. These dosage forms are also specifically advantageous for drugs either absorbed from the stomach or requiring local delivery in the stomach. Overall, these considerations led to the development of multiparticulate pulsatile release dosage forms possessing gastric retention capabilities. A multiparticulate floating-pulsatile drug delivery system was developed using porous calcium silicate (Flourite RE) and sodium alginate, for time and site-specific drug release of meloxicam for chronopharmacotherapy of rheumatoid arthritis. Meloxicam was adsorbed on the Flourite RE (FLR) by fast evaporation of solvent from drug solution containing dispersed FLR. [20-22]

LIMITATIONS:

1. Lack of manufacturing reproducibility and efficacy.
2. Large number of process variables
.3. Multiple formulation steps.
4. Higher cost of production.
5. Need of advanced technology.
6. Trained/ skilled personal needed for manufacturing. [23]

DISEASES REQUIRING PULSATILE DRUG DELIVERY SYSTEM

Circadian rhythm regulates many body functions in humans, viz., metabolism, behavior, Physiology, sleep patterns, hormone production, etc. Asthma is one such disease where pulsatile drug delivery system can be useful. Circadian changes are seen in normal lung function, which reaches a low point in the early morning hours. . In peptic ulcer, acid secretion is high in the afternoon and at night. In the case of cardiovascular diseases, BP is at its lowest during the sleep cycle and rises steeply during the early morning period. Platelet agreeability is increased, and fibrinolytic activity is decreased in the morning, leading to a state of relative hypercoagulability of the blood. Circadian increase in the blood sugar level after the meal has been observed in Diabetes mellitus. Circadian variations are seen in DOPA level in the afternoon in case of Attention deficit syndrome. [24]

ANKYLOSING SPONDYLITIS

Ankylosing spondylitis is characterized by swelling and discomfort of the joints of the back. In its occurrence, it is an inherited disorder that is more common in men than women. One investigator used questionnaires to study daily cycles in the back symptoms of 39 people suffering from this disease. Overall, back stiffness and pain were a problem throughout the 24h, but pain intensity was rated 2 to 3 times higher and stiffness about 8 times greater between 06:00 and 09:00 am than between noon and 15:00 pm when each was least bothersome. The symptoms also exhibited a second less prominent peak between 19:00 and 21:00 pm. The findings of a French study of 26 people suffering from this medical condition were identical. Ratings of the intensity of back stiffness and pain were higher in the morning and evening than in the afternoon. Marked seasonal variation in ankylosing spondylitis was also prominent. The onset of a backache and stiffness was 12 times more frequent in winter than summer. Moreover, reoccurrence of back problems occurs 2 to 3 times more often in winter than summer diseases as seen in Fig.3[25]

Figure 3: Early Ankylosing Spondylitis and advanced Ankylosing Spondylitis characterised by swelling and discomfort of joints of the back. Ratings of the intensity of back stiffness and pain were higher in the morning and evening than in the afternoon.

CARDIOVASCULAR DISEASE

In cardiovascular disease, capillary resistance and vascular reactivity are higher in the morning and decreases later in the day. Platelet agreeability is increased and fibrinolytic activity is decreased in the morning, leading to a state of relative hypercoagulability of the blood. Because of this reason, the frequencies of myocardial infarction and of sudden cardiac death are more during a period from morning to noon. Ambulatory blood pressure measurements show a significant circadian variation to characterize blood pressure. This variation is affected by a variety of external factors such as ethnicity, gender, autonomic nervous system tone, vasoactive hormones, hematological and renal variables. Increased heart rate, blood pressure, imbalanced autonomic tone, circulating level of catecholamine controlling the cardiac arrhythmias show important circadian variation and trigger the genesis of the circadian pattern of cardiac arrhythmias. Atrial arrhythmias appear to exhibit circadian pattern usually with a higher frequency in the daytime and lower frequency in the nighttime with the abnormal foci under the same long-term autonomic regulation as normal pacemaker tissue. According to study ventricular arrhythmias shows late morning peak in the patients with myocardial infarction sometime in the distant past morning peak and afternoon peak in patients with recent myocardial infarction. Cardiovascular diseases such as hypertension and angina, or chest pain, also follow a definite circadian rhythm[25-26]

HYPERTENSION

Heart rate and blood pressure are increased in the early morning hours (morning or A.M. surge). The blood pressure declines from mid-afternoon and is minimum at midnight. In most hypertensive patients, there is a rather marked rise in blood pressure upon awakening that is called the morning or "a.m." Systolic blood pressure rises approximately 3mm Hg/hour for the first 4-6 hours post-awakening, while the rate of rising of diastolic blood pressure is approximately 2mm Hg/hour[27]

MYOCARDIAL INFARCTION

The onset of myocardial infarction has been shown to be more frequent in the morning with 34% events occurring between6 A.M. and noon. Acute cardiac arrest and transient myocardial ischemia show an increased frequency in the morning. Myocardial infarction occurs when one of the arteries that supply the heart muscle becomes blocked. Bloclage may be caused by acute clot formation. The blockage results in damaged tissue and permanent loss of contraction of heart muscle. The causes for these findings have been suggested to be released of catecholamine, cortisol increase in the platelet and vascular tone The major objective of chronotherapy is to deliver the drug in higher concentration during time of greatest need (i.e. early in the morning) and lesser when the need is less (i.e. lower amount at night).1ACE inhibitors are more effective when administered during night. Atenolol, Nifedipine and amlodipine are more effective when administered at night. This is represented in Fig.4[28]

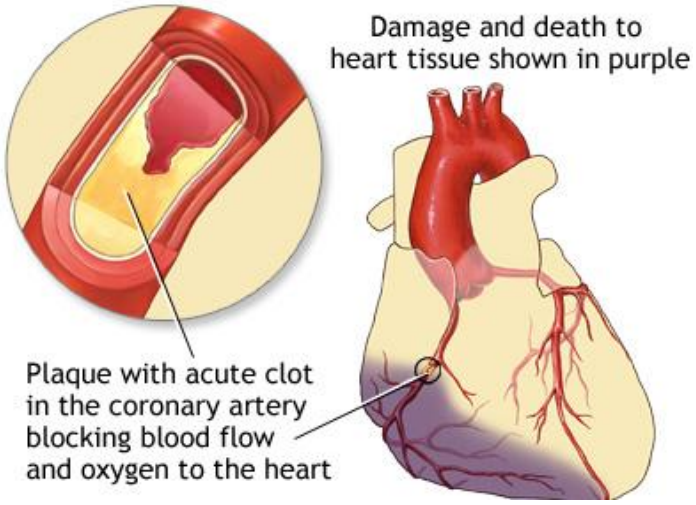

Figure 4: Myocardial infarction occurs when one of the arteries that supplies the heart muscle becomes blocked. Blockage may be caused by acute clot formation. The blockage results in damaged tissue and permanent loss of contraction of heart muscle.

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. Circadian changes are seen in normal lung function, the later reaches a low point in the early morning hours. This dip is particularly pronounced in people with asthma. Because bronchoconstriction 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 B2-agonists. [29]

BRONCHIAL ASTHMA:

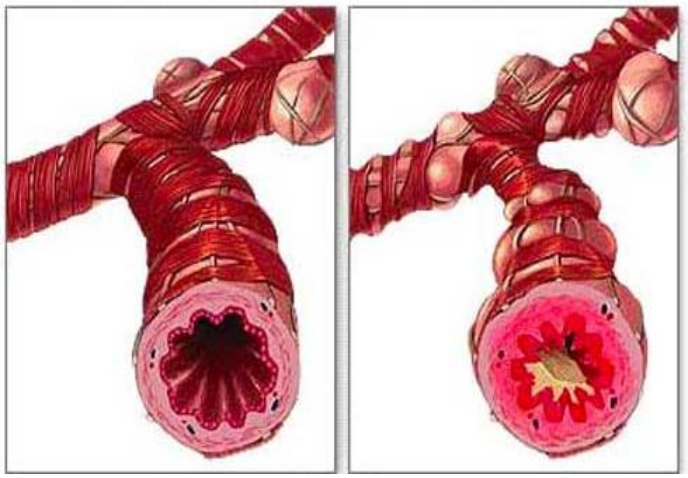

Figure5: Chronic inflammatory condition characterised by hyperresponsiveness to a variety of stimuli. Airways become inflamed, narrow and swell and produce extra mucus, which makes difficult to breath.

Bronchial Asthma is a chronic inflammatory disease of the airways, characterized by hyperresponsiveness to a variety of stimuli. The role of circadian rhythms in the pathogenesis and treatment of asthma indicates that airway resistance increases progressively at night in asthmatic patients. Circadian changes are seen in normal lung function, which reaches a low point in the early morning hours.6The worsening of asthma at night commonly referred to as nocturnal asthma (NA). A drug delivery system administered at bedtime but releasing drug during morning hours would be ideal in this case. [29]

DISEASES	CHRONOLOGICAL BEHAVIOUR	DRUGS
Peptic ulcer	Acid secretion is more in afternoon and night	H2 blockers
Cancer	The blood flow to tumors is threefold greater during each daily activity phase of the circadian cycle than during the daily rest phase.	Vinca alkaloids, Taxanes
Deuodenal ulcer	Gastric acid secretion is highest at night, while gastric and small bowel motility and gastric emptying are all slower at nigh	Proton pump inhibitors
Neurological disorder	The central pathophysiology of epilepsy and the behavioral classification of convulsive events.	MAB-O inhibitors
Hypercholesterolemia	Cholesterol synthesis is generally higher during the night than day time.	HMG CoA reductase inhibitors
Diabetes Mellitus	Increase in the blood sugar level after a meal.	Sulfonylurea , insulin
Arthritis	Level of pain increases at night.	NSAIDS, Glucocorticoids
Cardiovascular diseases	BP is at its lowest during the sleep cycle and rises steeply during the early morning	Nitroglycerin, calcium channel blocker, ACE inhibitors
Asthma	Precipitation of attacks during the night or at early morning.	B2 agonist, antihistamines
Attention deficit syndrome	Increase in DOPA level in the afternoon.	Methylphenidate

RECENT ADVANCES IN PULSATILE DRUG DELIVERY SYSTEMS:

Nowadays pulsatile drug delivery systems are gaining importance in various disease conditions specifically in diabetes where dosing is required at different time points. Among these systems, multi-particulate systems (e.g. pellets) offer various advantages over the single unit which include no risk of dose dumping, the flexibility of blending them with different release patterns, as well as short and reproducible gastric residence time. Multiparticulate systems consist pellets of different release profile which can be of any type like time-dependent, pH-dependent, microflora activated system as discussed in the previous sections. Site and time specific oral drug delivery has recently been of great interest in the pharmaceutical field to achieve improved therapeutic efficacy. Gastroretentive drug delivery system is an approach to prolong gastric residence time, thereby targeting site-specific drug release in upper gastrointestinal (GI) tract. [30]

CURRENT SITUATION AND FUTURE SCOPE

Now a day's pulsatile drug delivery is gaining popularity. The prime advantage in this drug delivery is that drug is released when necessity comes. As a result, chance of development of drug resistance which is seen in conventional and sustained release formulations can be reduced. Furthermore, some anticancer drugs are very toxic. These drugs give hazardous problems in conventional and sustained release therapies. Now many FDA approved chronotherapeutic drugs are available in the market. This therapy is mainly applicable where sustained action is not required and drugs are toxic. The key point of development of this formulation is to find out circadian rhythm i.e. suitable indicator which will trigger the release of drug from the device. Another point is the absence of suitable. Another biomaterial which should be biodegradable, biocompatible and reversibly responsive to specific biomarkers in a rhythmic manner. Regulatory is another big question. In pre-approval phase, it is sometimes difficult to show a chronotherapeutic advantage in clinical settings. In post-approval phase causal recreational drug abuse along with on a much larger scale, by the criminal diversion of these modified formulations for profit have arisen problems. The FDA has now heavily relied on the development and implementation of risk management programs as a strategy to allow the approval of a drug to go forward while exercising some restrictions. Many types of research are going on the pulsatile drug delivery to discover circadian rhythm with a suitable device in the world. In future, this delivery will be a leading way to deliver therapeutic agents due to its some unique characters like the low chance of dose dumping, patient compliance, and the above factors. [31]

CONCLUSION

The literature review relating to this formulation strongly recommending the constant need for new delivery systems that can provide increased therapeutic benefits to the patients. Pulsatile drug delivery is one such system that, by delivering a drug at right time, right place, and in right amounts, holds good promises of benefit to the patients suffering from chronic problems like ankylosing spondylitis, asthma, hypertension, etc. Extended-release formulations and immediate release formulation are not effective in treating the diseases especially diseases with chronological pathophysiology, for which, pulsatile drug delivery is beneficial. The drug is delivering in this system when its actual concentration is needed as per chronological need, so pulsatile release systems should be promising in the future.

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