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Research Article

PULSATILE DRUG DELIVERY SYSTEM: NOVEL APPROACH TO TARGET THE DIFFERENT DISEASES INCLUDING CANCER

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A B S T R A C T

As we know malignancy is most familiar as a characterization of cancer, a malignant tumor contrasts with a non-cancerous benign tumor in that a malignancy is not self-limited in its growth, is capable of invading into adjacent tissues, and may be capable of spreading to distant tissues. Malignancy in cancers is characterized by anaplasia, invasiveness, and genome instability, so that cancers, as assessed by whole genome sequencing, frequently have between 10,000 and 100,000 mutations in their entire genomes. Cancers usually show tumor heterogeneity, containing multiple sub clones, frequently have reduced expression of DNA repair enzymes due to epigenetic methylation of DNA repair genes or altered micro RNAs that control DNA repair gene expression.

As we move to pulsatile system it releases the drug completely after defined lag time, system is time and site-specific, thus providing special and temporal drug delivery and increasing bioavailability. Targeting malignancy/ cancer, specific drug at site of action requires the specific drug delivery techniques and pulsatile drug delivery is one of them.

The delivery of drugs specifically to the site without being absorbed first in the upper gastrointestinal (GI) tract allows for a higher concentration of the drug to reach the site with minimal systemic absorption. A drug can be delivered to the site via the oral, or the rectal route, as oral dosage forms are the most preferred delivery route for site-specific delivery due to their convenience these forms also allow for a greater degree of flexibility in their manufacturing, design, improved patient adherence & relatively safe administration.

INTRODUCTION

Oral drug delivery is the largest segment of the total drug delivery market. It is the most preferred route for drug administration. The oral controlled-release systems show a typical pattern of drug release in which the drug concentration is maintained in the therapeutic window for a prolonged period of time, thereby ensuring sustained therapeutic action. There are certain conditions for which such a release pattern is not suitable that demand release of a drug after a lag time. In other words, they require pulsatile drug delivery system (PDDS).[1]

Pulsatile Drug Delivery Systems are gaining a lot of interest as they deliver the drug at the right place at the right time and in the right amount, thus providing spatial, temporal and smart delivery and increasing patient compliance. These systems are designed 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.[2]

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Various systems like capsular systems, osmotic systems, single and multiple-unit systems based on the use of soluble or erodible polymer coating and use of rupturable membranes have been dealt with in the article. It summarizes the latest technological developments, formulation parameters, and release profiles of these systems. When we talk about the treatment of cancer by using Pulsatile drug delivery system it offers the blood flow to tumors is 3-fold greater during each daily activity phase of the circadian cycle than during the daily rest phase.

Colon Cancer is an alarming health problem worldwide. It is the third most common cancer in men and the second most common in women. In India, the annual incidence rates (AARs) for colon cancer and rectal cancer in men are 4.4 and 4.1 per 100000, respectively. The AAR for colon cancer in women is 3.9 per 100000. Colon cancer ranks 8th and rectal cancer ranks 9th among men for women, rectal cancer does not figure in the top 10 cancers, whereas colon cancer ranks 9. Many factors are involved for colon cancers which include age, sex, obesity, smoking, diabetes mellitus and others. Colon cancer is a cancer of the large intestine (colon), which is the final part of your digestive tract it begin as small, noncancerous (benign) clumps of cells called adenomatous

polyps. Over time some of these polyps can become colon cancers.[3]

There are numerous advantages of this system used for treatment of cancer, some of them are

1. Ability to release drug in a burst manner, it increases absorption and bioavailability at target site of absorption.
2. Limit risk of mucosal irritation.
3. Loss of drug by extensive first pass metabolism is prevented.
4. Chronotherapy, programmed delayed release provides optimal treatment of diseases.
5. No risk of dose dumping.
6. Decreases drug interaction due to lower cytochrome P450 is enzymes.
7. Avoidance of undesirable side effects.
8. Improved patient compliance & Flexibility in design.

The colon is a site where both local and systemic delivery of drugs can take place. Local delivery allows topical treatment of many diseases and the treatment could be made more efficient if it was possible for drugs to be targeted like a shot to the colon[8]

Technical Information

Colonic delivery refers to targeted delivery of drugs into the lower gastrointestinal tract, which occurs primarily in the large intestine (i.e. colon). The colon is a site where both local and systemic delivery of drugs can take place. Local delivery allows topical treatment of inflammatory bowel disease and systemic drug delivery are mainly used for to treat the hypertension. However, treatment can be made effective if the drugs can be targeted directly into the colon, thereby reducing the systemic side effects.

Targeted drug delivery into the colon is highly desirable for hypertension. The colon specific drug delivery system protects the drug i.e. drug release and absorption doesn't occur in the stomach and in the small intestine. The colon is believed to be a suitable absorption site for peptides and protein drugs due to less diversity and intensity of digestive enzymes and comparative proteolytic activity of colon mucosa less than that observed in the small intestine.

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Colon specific delivery protects peptide drugs from hydrolysis, and enzymatic degradation in duodenum and jejunum, and eventually releases the drug into ileum or colon which leads to greater systemic bioavailability. The colon having long residence time up to 5days is highly responsive to absorption enhancers.

Site-specific delivery to colon is advantageous in developing many pharmaceutical products and also useful for the absorption of drugs which are poorly soluble. Colon is mostly advantageous as it has slow transit time, less fluid volume, less digestive enzymes with less motility.

Colon specific delivery ensures direct treatment at disease site with lower dosing and less systemic side effects. Entry of drugs into systemic circulation can also occur via the colon. Not only drug solubility but also the stability of drug in colonic environment is a further factor that warrants attention. The drug could bind in a nonspecific manner to dietary residues, intestinal secretions, mucus or general fecal matter, where the concentration of drug may get reduced. Moreover, the resident micro-flora could also affect colonic performance via degradation of the drug. Colonic delivery refers to targeted delivery of drugs into the lower gastrointestinal tract, which occurs primarily in the large intestine (i.e. colon). The colon is a site where both local and systemic delivery of drugs can take place. Local delivery allows topical treatment of inflammatory bowel disease and systemic drug delivery are mainly used for to treat the hypertension. However, treatment can be made effective if the drugs can be targeted directly into the colon, thereby reducing the systemic side effects.

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The oral route is considered to be most convenient for the administration of drugs to patients. Oral delivery of drugs to the colon is valuable in the treatment of colon diseases (ulcerative colitis, crohn's disease, carcinomas and infections) whereby high drug concentration can be achieved while minimizing side effect that occur because of release of drugs in the upper GIT or unnecessary systemic absorption. The colon is rich in lymphoid tissue, uptake of antigens into the mast cells of the colonic mucosa produces rapid local production of antibodies and this helps in efficient vaccine delivery. As colon is the distal segment of the large intestine, hence targeting the drug to the colon is very problematic, so the rectal route can also be used for the colon delivery but it has

some limitations of limited transit of the drug in the intestinal passage. Moreover the rectal route is not easy and unacceptable by the patient. [4]So the oral route is most preferred. Colon targeted drug delivery is an example of controlled drug delivery system.

This system focused mainly on site specificity via release of bioactive drug in colon and absorption from the same. Colon targeted drug delivery differs from ordinary enteric coating (that are designed to merely avoid drug release in the stomach) in that the tablet or capsule is specially formulated to channel greater quantity of drug release to the colonic compartment, thus preventing or reducing drug release until the dosage form reaches the colon . Although the large intestine is difficult to access through per oral delivery it is still favored as the appropriate site to tackle local colon related diseases.[5,6]

The colon is a site where both local and systemic drug delivery can take place. It is also preferred as an absorption site for oral administration of peptides drugs, because of the comparatively less hostile environment and low proteolytic enzyme activities in the colon.

Colon act as Black-box of the body and site specificity is difficult task. Various factors to be considered for designing colon specific drug delivery.[7]

Studies of colonic motility, in vivo, usually on measurement of changes in muscle electrical activity that may determine contractions. Manometer measure changes in colonic pressure caused by contractions and/or strain gauges measure contractions more directly. All approaches provide useful information but when used separately may not give a complete picture of colonic motor events.[9, 10] Electrical activity may not produce measurable contraction and manometric techniques can only detect contractions that occlude the lumen sufficiently to register as an increase in pressure. In vitro measurements using strips or segments of colon may suggest mechanisms and patterns of electrical and motor activity, but their role must be assessed in vivo in an intact colon with enteric and autonomic nervous system (ANS) and central nervous system (CNS) connection maintained. Since in vivo studies in human involve intubations and often bowel cleansing (sometimes with cathartics that may sensitize the colon), it is difficult to assess whether the same patterns would be seen without the invasive tubes and with a colon full of chemically and mechanically stimulating content.[11]

Different Approches Used For Colon Targeting [12,13,14,15]

Pro drug approach

Prodrug is pharmacologically inactive derivative of a parent drug molecule that requires biotransformation in vivo to release the active drug from the carrier. The enzymes like azoreductase, galactosidase, xylosidase, nitroreductase, glycosidase and deaminase are mainly targeted for colonic drug delivery. Prodrug targeted drug delivery system include three components: a drug, a carrier, targeting moiety. This approach shows promising results in the colon drug delivery system as it minimize absorption of active drug from the upper GI tract.

Pro Biotic Approach

The Probiotic approach is one of the latest approach for colon targeting. In this approach, three components are desirable namely probiotic strain, microbially digestable carrier and triggering temperature. Probiotic strains include inactive microflora like Bifidobacterium and Lactobacillus species. At body temperature, these strains triggered to be active and start digesting the carrier and ultimately release the drug at desired place. This approach gain success in colon drug delivery system because these conditions are only available in colon.

Hydrogel Approach

Hydrogels incorporating drugs was also found to be used as oral colon drug delivery devices. Many studies show that this system has significant potential. Various type of hydrogel based CDDS were reported by different researchers. These are of three types, namely azo cross-linked, alcohol cross-linked and aldehyde cross-linked hydrogels.

pH-dependent Approach

During fasting the pH range of the stomach is in between 1-2 but on eating its increases. The pH of proximal small intestine is about 6.5 and in the cecum are about 6.4. However, pH values as low as 5.7 has been measured in the ascending colon in healthy volunteers. The pH in the transverse colon is 6.6 and in the descending colon 7.0 (Koteshwara *et al*., 2011). Colon targeted drug delivery systems based on meth acrylic resins has described for insulin, prednisolone, quinolones, cyclosporine, salsalazine, beclomethasone dipropionate and naproxane (Modasiya and Patel, 2011). The principle in this method is the coating of the tablets/pellets etc with various pH sensitive polymers which will produce delayed release and also give protection from gastric fluids.

Time Dependent Approach

In this approach, the basic principle is the release of the drug after a predetermined lag time from dosage form at the site of action at right time and in right amount (Wasnik and Parmar, 2011). Both large single-unit formulations and small multiple-unit formulations take three to four hours to pass through the small intestine, that can be unaffected by particle size, density or composition of the meals, because the time taken to leave the formulation to the stomach was not predicted.

Microbial Triggered Approach

The basic principle involved in this method is degradation of coated polymers on the drug delivery system by microflora present in colon and release of drug in colonic region. The microflora of the colon is in the range of 1011-1012 CFU/ml consisting mainly of anaerobic bacteria, e.g. Bacteroides Bifidobacterium, Eubacteria, Clostridia, Enterococci, Enterobacteria and Ruminococcus etc

This approach is different from probiotic approach because in probiotic approach, we are providing microflora from external source which assist the interior flora.

CODES^{TM}

This technology was introduced to avoid viscero-colonic problems associated with time or pH. CODESTM is a combinational approach of microbially triggered and pH dependent CDDS. It has been developed for the site specific release in the colon by utilization of a unique triggered mechanism involving lactulose. In this system, lactulose is incorporated in the core, followed by coat of Eudragit E which is acid soluble in nature and then subsequently overcoated with an enteric material, Eudragit L. Outermost coat of Eudragit L protect the ultimate tablet to be dissolved in gastric fluids and

former Eudragit protects the preparation as it passes through the alkaline pH of the small intestine. Microbial triggered degradation of lactulose starts when the tablet arrives in the colon.

Osmotic controlled drug delivery (ORDS-CT)

A novel CDDS was introduced by Alza Corporation, to target the drug locally to the colon, which is known as OROS-CT. The OROS-CT system include either single osmotic unit or upto 6 push pull units, each 4 mm in diameter, encapsulated within a hard gelatin capsule.

PULSINCAP System

This technique was introduced by R.R.Scherer International Corporation, Michigan, US, to target water insoluble capsules. This formulation possess seal coat with swellable hydrogel plug to enclosing the drug reservoir into the capsule body. At particular lag time, capsule was come to in contact with dissolution fluid, swelling take place and drug release rapidly.

PORT system

This technique was introduced by Therapeutic System Research Laboratory Arm Arbor, Michigan, USA, and consists of insoluble plug of drug and osmotically active agent coated with a semi permeable membrane of the capsule. System used to delivered methylphenidate to school age children and shows good in-vivo and in-vitro correlation in humans for the treatment of attention deficit hyper activity disorder (ADHD).

Time clock system

In this technique, an aqueous dispersion is used for coating of the solid dosage form. In this coating is a hydrophobic surfactant layer to which a water soluble polymer is added to improve adhesion to the core. The rehydration of the system results when it comes in contact with dissolution fluid, and redisperses also. In this system, the lag time could be controlled by proportional varying the thickness of the coating material.

Pressure controlled drug delivery system

Peristaltic movements of intestines along with gastric contractile activity are responsible for the propulsion of intestinal contents. These peristaltic movements constitute elevated luminal pressure conditions in the colon. The design of pressure controlled drug delivery system is based upon above mechanism. Intensity and duration of this pressure varies with the muscular contractions in the visceral organs.

Nanoparticulate system

Nanoparticle size colloidal carriers composed of natural or synthetic polymers have also been investigated for colon targeting. Orally administered nanoparticles serve as carriers for different types of drugs and have been shown to enhance their solubility, permeability and bioavailability. Nanoparticles have also been investigated for the delivery of protein and peptide drugs.

Multi particulate approach tried for colon delivery include formulations in the form of pellets, granules and microparticles. Researchers developed biodegradable colon targeted multi particulate system by using guar gum.

ETHICS

Pulsatile Drug Delivery Systems are gaining a lot of interest as they deliver the drug at the right place at the right time and in the right amount, thus providing spatial, temporal and smart delivery and increasing patient compliance. These systems are designed 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.[17] 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 and use of rupturable membranes have been dealt with in the article. It summarizes the latest technological developments, formulation parameters, and release profiles of these systems.[16] These systems are beneficial for the drugs having chronopharmacological behavior such as drug used in treatment of rheumatoid arthritis, osteo arthritis and ankylosing spondylitis like inflammatory disorders. Current review article discussed the reasons for development of pulsatile drug delivery system, types of the disease in which pulsatile release is required, classification, evaluations, advantages, limitation, and future aspects of pulsatile drug delivery system.

Chronopharmacokinetics involves 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.[19]

Technology	Mechanism	Proprietary name and dosage form	API	Disease
OROS®;	Osmotic Mechanism	Covera-HS® XL Tablet	Verapamil HCl	Hypertension
CODOS®	multiparticulate ph dependent system	Verelan® PM; XL release capsule	Verapamil HCl	Hypertension
DIFFUCAPS®	multiparticulate system	Innopran®;XL tablets	Verapamil HCl, propranolol HCl	Hypertension
Three dimensional printing®	externally regulated system	TheirForm®	Diclophenac sodium	Inflammation
PulsincapTM	Rupturable system	PulsincapTM	Dofetilide	Hypertension

Fig 1 Marketed formulation of pulsatile drug delivery system.

Biological Rhythms [20, 21]

Ultradian Rhythms

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

Infradian Rhythms

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

Circadian rhythms

Circadian rhythms are self-sustaining, endogenous oscillations that occur with a periodicity of about 24 Hours. Interestingly, the term circadian is derived from the Latin circa which means “about” and dies which can be defined as “a day”. Normally,

circadian rhythms are synchronized according to internal biologic clocks related to the sleep-wake cycle.

Recent Advances in the Pulsatile Drug Delivery

Nowadays pulsatile drug delivery systems are gaining importance in various disease conditions specifically in 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. Multiparticulate systems consists pellets of different release profile which can be of any type like time dependent, pH dependent, micro flora activated system as discussed in the previous sections. Site and time specific oral drug delivery have recently been of great interest in pharmaceutical field to achieve improved therapeutic efficacy. Gastroretentive drug delivery system is an approach to prolong gastric residence time, thereby targeting sitespecific drug release in upper gastrointestinal (GI) tract. Floating drug delivery system (FDDS) and bioadhesive drug delivery are widely used techniques for gastro retention.[22,23] Low density porous multiparticulate systems have been used by researchers for formulation of FDDS. Sharma and Pawar developed multiparticulate floating pulsatile drug delivery system using porous calcium silicate and sodium alginate for time and site specific drug release of meloxicam. Various pulsatile technologies have been developed on the basis of methodologies as discussed previously. These includes OROS® technology, CODAS® technology, CEFORM® technology, DIFFUCAPS® technology, Three dimensional printing®, timerx® etc.[24,25]

OROS® technology

Chronset™ is a proprietary OROS® delivery system that reproducibly delivers a bolus drug dose in a time- or site-specific manner to the gastrointestinal tract. It is nothing but osmosis based system. The active pharmaceutical is kept in a reservoir surrounded by a semipermeable membrane laser drilled with a delivery orifice and formulated into a tablet. There are two layers in this tablet comprising of one drug layer and another osmotically active agent. Upon contact with GI fluid this osmotic agent changes its characteristic from nondispensable to dispensable viscosity. As a result active pharmaceutical is pushed away through the channel due to pump effect of the osmotic agent. It is used generally for designing of extended release tablet.

CEFORM® technology

It produces uniformly sized and shaped microspheres of pharmaceutical compounds. This approach is based on “melt-spinning” which means subjecting solid feedstock (i.e. biodegradable polymer/ bioactive agent combinations) to a combination of temperature, thermal gradients, mechanical forces, flow and flow rates during processing. The microspheres obtained are almost perfectly spherical, having a diameter that is typically of 150–180 mm, and allow for high drug content. The microspheres can be used in a wide variety of dosage forms including tablets, capsules, suspensions, effervescent tablets and sachets. The microspheres may be coated for controlled release with an enteric coating or may be combined into a fast/slow release combination.

CONTIN® technology

Here cellulose polymer and a nonpolar solid aliphatic alcohol constitute molecular coordination complexes between them. At first that polymer is solvated with a polar solvent. Alcohol may be optionally substituted with an aliphatic group. This alcohol is added to the solvated polymer preferably as a melt. After addition it forms the coordination complex having utility as a matrix in controlled release formulations since it has a uniform porosity which may be varied. It is also applicable for designing of controlled release tablets. This technology has sufficient control over drug release to the blood and reduces the chances of unwanted side effects.

DIFFUCAPS® technology

This technology is nothing but capsule based system containing one or more drug-containing particles (e.g. beads, pellets, granules etc.). Each bead shows pre-programmed rapid or sustained release profile with or without lag time. It has been already discussed in system with erodible, soluble or rupturable membrane section.

CHRONOTOPIC® technology

It is also described in system with erodible, soluble or rupturable membrane system. It is basically drugcontaining core coated with an outer releasecontrolling layer. Both single and multiple-unit dosage forms such as tablets and capsules or minitablets and pellets have been employed as the inner drug formulation.

EGALET® technology

It is a delayed release form consisting of an impermeable shell with two lag plugs, enclosing a plug of active drug in the middle of the unit. After erosion of the inert plugs the drug is released. Time taken to erode the inert plugs determines the lag time. The shells are made of slowly biodegradable polymers (e.g. ethylcellulose) and plasticizers (such as cetostearyl alcohol), while the matrix of the plugs is a mixture of pharmaceutical excipients including polymers like polyethylene oxide (PEO).

CODAS® technology

Chronotherapeutic Oral Drug Absorption System (CODAS) technology is a multiparticular system designed for bedtime dosing. Here nonenteric coating is applied on drug-loaded beads to delay the release of drug up to 5 h. Here release controlling contains mixture of both water-soluble and waterinsoluble polymers. When this dosage form comes in contact with GI fluid water-soluble polymer gets dissolved slowly and pores are formed on the coating layer. Drug diffuses through these resulting pores.

TIMERx® technology

It is hydrogel based controlled release device. This technology can provide from zero order to chronotherapeutic release. It can provide different release kinetic by manipulating molecular interactions. The authors claimed that the “molecular engine” replaces the need for complex processing or novel excipients and allows desired drug release profiles to be “factory set” following a simple formulation development process. Basically, this technology combines primarily xanthan and locust bean gums mixed with dextrose. The physical interaction between these components works to form a strong, binding gel in the presence of water. Drug release is controlled

by the rate of water penetration from the gastrointestinal tract into the TIMERx gum matrix, which expands to form a gel and subsequently releases the active drug substance.

PORT® technology

The Programmable Oral Release Technologies (PORT) system is a uniquely coated, encapsulated system that can provide multiple programmed release of drug. It contains a polymeric core coated with a semipermeable, rate-controlling polymer. Poorly soluble drugs can be coated with solubilising agents to ensure uniform controlled release from the dosage form. In capsule form had gelatin capsule is coated with a semipermeable, rate-controlling polymer. Active medicament mixed with osmotic agent is kept inside capsule shell. A water-insoluble plug is used to seal the capsule shell. Immediate release compartment can be added according to need.[26, 27, 28]

Evaluation test of Pulsatile Drug Delivery System

- ✓ Preformulation study
- ✓ Drug excipients interaction study
- ✓ Evaluation of granule
- ✓ Tablet Thickness
- ✓ Uniformity of weight
- ✓ Hardness/ Crushing strength
- ✓ Evaluation of polymeric film
- ✓ In vitro dissolution study Comparison of dissolution profiles
- ✓ In vivo study of prepared formulation
- ✓ Anti-inflammatory activity study

Current & Future Scope

Pulsatile drug delivery systems (PDDS) can be classified in site-specific and time-controlled systems. Drug release from site-specific systems depends on the environment in the gastro intestinal tract, e.g., on pH, presence of enzymes, and the pressure in the gastro intestinal tract. In contrast, time-controlled DDS are independent of the biological environment. The drug release is controlled only by the system. Time-controlled pulsatile delivery has been achieved mainly with drug-containing cores, which are covered with release-controlling layers

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. 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 absence of suitable rhythmic biomaterial which should be biodegradable, biocompatible and reversibly responsive to specific biomarkers in rhythmic manner. Regulatory is another big question. In preapproval phase it is sometimes difficult to show 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. [29, 30, 31]

The FDA has now heavily relied on the development and implementation of risk management programs as a strategy to allow an approval of a drug to go forward while exercising some restrictions. Many researches are going on the pulsatile drug delivery to discover circadian rhythm with 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 low chance of dose dumping, patient compliance and the above factors.[32, 33]

CONCLUSION

The most critical challenge in oral colon specific drug delivery approach is to preserve the formulation during its passage through the stomach and about six meters of the small intestine. After seeking the limitations of different approaches, researchers invented various novel approaches which act as remedy for the previous ones. Now several approaches have been investigated to achieve site specificity to colon. The selection of suitable carrier and/or coating system is a critical parameter in the fabrication of colon specific drug delivery. Novel approaches like Probiotic assisted, CODESTM, Nanoparticulate system etc. showed significant potential in this area. Also, other having vivid types of advantages in them. These recent advances in CDDS have promoted targeting of drugs and peptides in the treatment and management of major diseases and infections of the colon.

The literature review relating to this formulation strongly recommending 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 arthritis, asthma, hypertension, etc. Extended release formulations and immediate release formulation are not efficient in treating the diseases especially diseases with chronological pathopysiology, 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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