Pulsatile drug delivery system for treatment of various Inflammatory Disorders: A Review

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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 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. 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. 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.

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1 INTRODUCTION[1-6]

Over the last 30 years the pharmaceutical market has been demonstrated increasing preferably for controlled and targeted drug delivery system. Such systems have been focused on constant, variable; sustain drug release and/or targeting the therapeutic

agent to a specific site/tissue/ organ. However, recently there are certain conditions for which such release pattern is not suitable. Such conditions that lead to the requirements of a time programmed therapeutic system, which capable of releasing drug after predetermined time delay and maintain constant drug levels throught the day. To introduce the concept of chronotherapeutics, it is important to define the following concepts.

Chronobiology: [4,5]

Chronobiology is the science concerned with the biological mechanism of the diseases according to a time structure. *"Chrono"* pertains to time and *"biology"* pertains to the study, or science, of life.

Chronopharmacology: [4,5]

Chronopharmacology is the science concerned with the variations in the pharmacological actions of various drugs over a period of time of the day.

Chronopharmacokinetics: [4,5]

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.

Chronotherapy: [4,5]

Co-ordination of biological rhythms and medical treatment is called chronotherapy.

Chronotherapeutics: [4-6]

Chronotherapeutics is the discipline concerned with the delivery of drugs according to inherent activities of a disease over a certain period of time. it is becoming increasingly moreevident that the specific time that patients take their medication may be even more significant than was recognized in the past.

2. BIOLOGICAL RHYTHMS: [7,8]

1. Ultradian Rhythms:

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

2. Infradian Rhythms:

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

3. 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. [7,8]

DISEASES AND CHRONOTHERAPEUTICS:

The potential benefits of chronotherapeutics have been demonstrated in the management of a number of diseases. In particular there is a great deal of interest in how chronotherapy can particularly benefit patients suffering from allergic rhinitis, rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, asthma, cancer, cardiovascular diseases, and peptic ulcer disease. [6]

Table: 1 Disease Influenced by Chronotherapy [6]

Diseases	Influenced by Chronotherapy
Cardiovascular	Hypertension, angina, myocardial infarction
Inflammatory	Rheumatoid arthritis, related disorders
Neoplastic	Various forms of cancer
Gastrointestinal	Peptic ulcer disease
Respiratory	Allergic rhinitis, asthma

Rheumatoid Arthritis

Rheumatoid arthritis is a chronic inflammatory autoimmune disorder. The cardinal signs of rheumatoid arthritis are stiffness, swelling and pain of one or more joints of the body characteristically most severe in the morning. Rheumatoid arthritis

shows a marked circadian variation in its symptoms [9, 10]. A group of British volunteers self-assessed the pain and stiffness of affected finger joints every 2 to 3 h daily for several consecutive days. They also measured the circumference of the arthritic joints to gauge the amount of their swelling, and they performed grip strength tests to determine the effect of the arthritic condition on the hands [11, 12]. Ratings of the severity of joint pain swelling and stiffness were about 3 times higher between 08:00 and 11:00 am than at bedtime. In contrast, hand strength was lower by as much as 30% in the morning than at night. This is typical of rheumatoid arthritis sufferers [13-15].

The symptoms of rheumatoid arthritis are always worse in the morning. Taking long-acting Non Steroidal Antiinflammatory Drugs (NSAIDs) like flubiprofen, ketoprofen and indomethacin at bedtime optimizes their therapeutic effect and minimizes or averts their side effects. 12-hour sustained-release NSAIDs that are taken twice a day must include a night or bedtime ingestion time to ensure adequate control of the prominent morning symptoms of rheumatoid arthritis. If the arthritic condition is severe, synthetic corticosteroids are often of benefit. Morning once-a-day dosing of these medicines is least likely to cause side effects especially if they are taken for a long period of time. Splitting the daily dose of medicine into several small ones for ingestion with meals and at bedtime or taking the entire daily dose at night is not recommended unless absolutely necessary. The risk of severe side effects from these medications increases when they are taken more than 8 to 9 h after the customary time of awakening, after 15:00 pm for most people. The later in the day these medications are taken, the greater the risk of side effects. If the relief from the morning symptoms of rheumatoid arthritis sufferers is not attained by a once-day morning schedule, an increase in the morning dose is recommended. The results of one study suggest an early afternoon once-a-day treatment schedule might be beneficial for those people who fail to get significant relief from the morning pain and stiffness of rheumatoid arthritis when taking medicine in the morning.

Osteoarthritis

The circadian rhythm of pain and stiffness in osteoarthritis differs from that of rheumatoid arthritis. Osteoarthritis is a degenerative disease of the joints and is the commonest of all joint diseases, affecting nearly everyone at least to some degree by age 70. The weight bearing joints of the hip, knee, back, toes and fingers are mostly affected. The pain of osteoarthritis sufferers is typically less intense in the morning than in the afternoon or evening. This is illustrated by the findings of a Canadian study of 20 persons troubled with osteoarthritis of the knee. Participants did pain self-ratings 10 times daily for 7 consecutive days. For the group as a whole, pain intensity was rated about 40 percent higher on average between 20:00 pm and midnight than between 06:00 and 10:00 am. However, the exact nature of the 24 h pattern of pain differed from person to person. In 40 percent, pain was greatest between 14:00 and 20:00 pm, and in 25%, it was highest between 20:00 pm and midnight. In 15 %, it peaked at two different times of the day, and in 20 %, the level of pain exhibited no day-night variation whatsoever. Interestingly, 40 % of the people exhibited weekly rhythms in pain intensity, although the exact day of the week it was worse varied. In some, it was more intense at the end of the week and in others the beginning. In summary, the day-night cycle of pain in osteoarthritis varies from one individual to another. Some experience worse pain in the morning and others at night. Some experiences two peaks i.e. in the morning and evening, while still others experience pain of equal intensity throughout the 24 h. The successful treatment of osteoarthritis requires that medications be taken at the right time

relative to the day-night pattern of pain in each person.

The temporal pattern of pain and stiffness in osteoarthritis sufferers differs between persons. Thus, an individualized chronotherapy of NSAIDs is necessary. The chronotherapy of osteoarthritis involves the administration of once-a-day forms of ketoprofen, indomethacin and other such medicines in relation to the time of day pain is worse. If pain is worse at night or early in afternoon, an evening once-a day NSAIDs schedule is recommended. If pain is worse in the afternoon or night, a once-a-day morning or noontime treatment schedule is best, providing the amount of side effects produced by the morning one, in particular, is minimal [16, 17].

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 24 h, 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 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 [18,19].

Table 2: Marketed technologies of pulsatile drug delivery [20-23]

Technology	Mechanism	Proprietary name and dosage form	API	Disease	References
OROS*	Osmotic mechanism	Covera-H5*; XL tablet	Verapamil HCL	Hypertension	20
Three dimentional printing*	Externally regulated system	Their Form*	Diclofenac sodium	Inflammation	21
DIFFUCAPS*	Multiparticulate system	Innopran*; XL tablets	Verapamil HCL, propranoll HCL	Hypertension	22
PulsincapTM	Rupturable system	PulsincapTM	Dofetilide	Hypertension	23

3. CLASSIFICATION OF PULSATILE DRUG DELIVERY SYSTEMS:[24]

A. Various approaches of pulsatile drug:

Pulsatile drug delivery system can be broadly classified into three classes;

I. Time controlled pulsatile drug delivery

II. Stimuli induced pulsatile drug delivery

III. Externally regulated pulsatile drug delivery

I. Time controlled pulsatile drug delivery

A. Single unit pulsatile systems

1. Capsule based systems

    E.g. Pulisincap system

2. Capsular system based on Osmosis

    a. 'PORT' System

    b. System based on expandable orifice

    c. Delivery by series of stops.

    d. Pulsatile delivery by solubility modulation

3. Pulsatile system with Erodible or soluble barrier coatings.

    a. The chronotropic system

b. 'TIME CLOCK' System.

c. Compressed tablets

d. Multilayered Tablets

4. Pulsatile system with rupturable coating

B. Multiparticulate / Multiple unit systems:

1. Pulsatile system with rupturable coating

E.g. Time –controlled Explosion system (TCES)

2. Osmotic based rupturable coating system

E.g. Permeability controlled system

3. Pulsatile delivery by change in membrane permeability

E.g. Sigmoidal release system.

II. Stimuli induced pulsatile drug delivery

1. Temperature-induced pulsatile release:

2. Chemical stimuli-induced pulsatile release:

* Glucose-responsive insulin release devices

* Inflammation-induced pulsatile release

* Drug release from intelligent gels responding to antibody concentration.

* Electric stimuli-responsive pulsatile release:

III. Externally regulated pulsatile drug delivery:

A. Single unit pulsatile systems

1. Capsule based 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. [25]
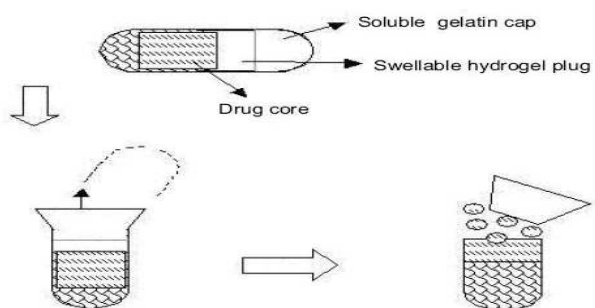
Fig 1: Design of Pulsincap system [25]

The lag time can be controlled by manipulating the dimension and the position of the plug. [26,27]

Polymers used for designing of the hydrogel plug

1) Insoluble but permeable and swellable polymers (e.g., polymethacrylates)

2) Erodible compressed polymers (e.g., hydroxypropylmethyl cellulose, polyvinyl alcohol, Polyethylene oxide)

3) Congealed melted polymers (e.g., saturated polyglycolated glycerides, glyceryl monooleate)

4) Enzymatically controlled erodible polymer (e.g., pectin). [28,29]

The preparation and invitro release of tetramethylpyrazine phosphate pulsincap capsule has been reported. It was prepared by sealing the drug tablet and fillers inside an impermeable capsule body with erodible plug. To meet the chronotherapeutic requirements, a suitable lag time can be achieved by adjusting the content of gel-forming polymer (HPMC) and the erodible plug weight. [30]

2. Capsular system based on Osmosis
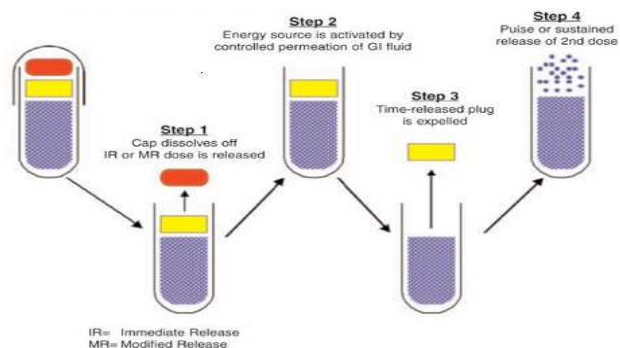
a. 'PORT' System [31]

Fig 2: Drug release mechanism from PORT system [31]

The Port system fig. (2) was developed by Therapeutic system research laboratory Ann Arbor, Michigan, USA, and consists of a capsule coated with a semipermeable membrane. Inside the capsule was an insoluble plug consisting of osmotically active agent and the drug formulation. [31] When this capsule came in contact with the dissolution fluid, the semipermeable membrane allowed the entry of water, which caused the pressure to develop and the insoluble plug expelled after a lag time. Such a

system was utilized to deliver methylphenidate used in the treatment of attention deficit hyperactivity disorder as the pulsatile port system. This system avoided second time dosing, which was beneficial for school children during daytime.

b. System based on expandable orifice: [32-34]

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 semipermeable capsule supported by an expanding osmotic layer after the barrier layer is dissolved. [32]
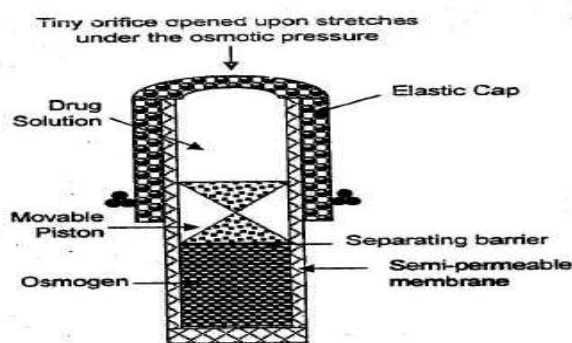

Fig. 3: System based on expandable orifice [32]

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. E.g. Elastomers, such as styrene-butadiene copolymer have been suggested. [33,34]

c. Delivery by series of stops: [35]

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. [35]

d. Pulsatile delivery by solubility modulation: [36-38]

Such systems contain a solubility modulator for pulsed delivery of variety of drugs. The system was especially developed for delivery of salbutamol sulphate. [36-38] The compositions contains the drug (salbutamol sulphate) and a modulating agent (sodium chloride). 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. Salbutamol has solubility of 275mg/ml in water and 16 mg/ml in saturated solution of NaCl, while NaCl has solubility of 321 mg/ml in water, and its saturation solubility is 320 mg/ml.

3. Pulsatile system with Erodible or soluble barrier coatings: [39-44]

Most of the pulsatile drug delivery systems are reservoir devices coated with a barrier layer. This barrier erodes or dissolves after a specific lag period, and the drug is subsequently released rapidly from reservoir core. The lag time depends on the thickness of the coating layer.
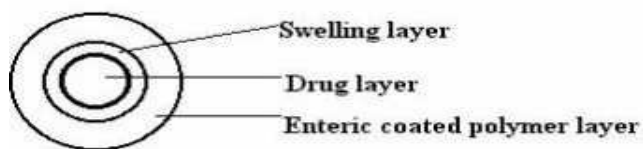
a. The chronotropic system: [39-44]

Fig. 4: The chronotropic system [39-41]

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.[39-41] 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.[42] The lag time is controlled by the thickness and the viscosity grades of HPMC.[43] Both *in-vitro* and *in-*

vivo lag times correlate well with the applied amount of the hydrophilic retardin polymer. The system is suitable for both tablets and capsules.[44]

b. 'TIME CLOCK' System: [39-44]

Solid salbutamol drug formulation → Coating with hydrophobic surfactant and water soluble polymer → Redispersion of polymer and drug release
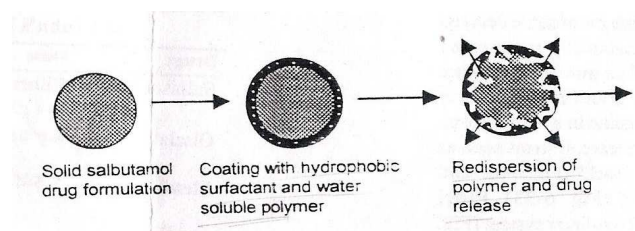
Fig.5: 'TIME CLOCK' System [39-44]

The lag time could be controlled by varying the thickness of the film. After the lag time, i.e., the time required for rehydration, the core immediately releases the drug. This system has shown reproducible results *in vitro* and *in vivo*. The effect of low calorie and high calorie meal on the lag time was studied using gamma scintigraphy. The mean lag time of drug release was 345 and 333 min respectively.[39-44]

c. Compressed Tablets: [45]

Compression coating can involve direct compression of both the core and the coat, obviating needs for separate coating process and use of coating solutions. The outer tablet of the compression-coated tablet provides the initial dose, rapidly disintegrating in the stomach and the inner layer is formulated with components that are insoluble in gastric media but are released in the intestinal environment. [45] Materials such as hydrophilic cellulose derivates can be used. Compression is easy on laboratory scale. The major drawbacks of the technique are that relatively large amounts of coating materials are needed and it is difficult to position the cores correctly. [45]

Press-coated pulsatile drug delivery systems:

1. Press-coated pulsatile drug delivery systems can be used to protect hygroscopic, light-sensitive, oxygenlabile or acid-labile drugs.

2. Press-coated pulsatile drug delivery systems are relatively simple and cheap.

3. These systems can involve direct compression of both the core and the coat.

4. Materials Such as hydrophobic, hydrophilic can be used in press-coated pulsatile drug delivery system.

5. Press-coated pulsatile drug delivery systems involve compression which is easy on laboratory scale.

6. Press-coated pulsatile formulations relese drug after "lag-time".

7. Press-coated pulsatile drug delivery formulations can be used to separate incompatible drugs from each other or to achieve sustained release.

d. Multilayered Tablets: [46-48]

Drug III —
Drug II —
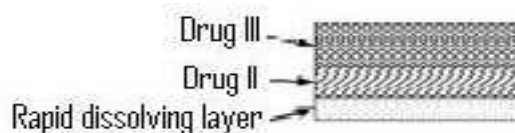Rapid dissolving layer —

Fig.6: Multilayered Tablet [46-48]

A release pattern with two pulses was obtained from a threelayered tablet containing two drug containing layers separated by a drug-free gellable polymeric barrier layer. [46-48]

4. Pulsatile system with rupturable coating: [49]

These systems depend on the disintegration of the coating for the release of drug. The pressure necessary for the rupture of the coating can be achieved by the effervescent excipients, swelling agents, or osmotic pressure. An effervescent mixture of citric acid and sodium bicarbonate was incorporated in a tablet core coated with ethyl cellulose. The carbon dioxide developed after penetration of water into the core resulted in a pulsatile release of drug after rupture of the coating. [49] The release may depend on the mechanical properties of the coating layer. [49]

a) Pulsatile system based on rupturable coating: [49-52]

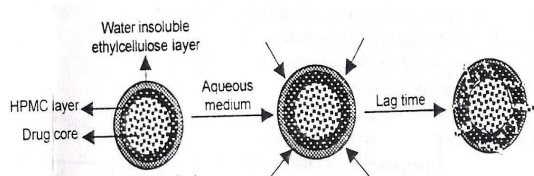E.g. Time –controlled Explosion system (TCES):

Fig.7: Time –controlled Explosion system (TCES) [49-51]

This is a multiparticulate system in which drug is coated on non-pareil sugar seeds followed by a swellable layer and an insoluble top layer.[50-52] The swelling agents used include Superdisintegrants like sodium carboxymethyl cellulose, sodium starch glycollate, L hydroxypropyl cellulose. Polymers like polyvinyl acetate, polyacrylic acid, polyethylene glycol, etc.

a) Osmotic based rupturable coating system: [53]

This system is based on a combination of osmotic and swelling effects. The core containing the drug, a low bulk density solid and/or liquid lipid material (eg, mineral oil) and a disintegrant was prepared. This core was then coated with cellulose acetate. Upon immersion in aqueous medium, water penetrates the core displacing lipid material. After the depletion of lipid material, internal pressure increases until a critical stress is reached, which results in rupture of coating. [53]

b) Pulsatile delivery by change in membrane permeability: [54,55]

The permeability and water uptake of acrylic polymers with quaternary ammonium groups can be influenced by the presence of different counter-ions in the medium. [54] Several delivery systems based on this ion exchange have been developed. Eudragit RS 30D is reported to be a polymer of choice for this purpose. It typically contains positively polarized quaternary ammonium group in the polymer side chain, which is always accompanied by negative hydrochloride counter-ions. The ammonium group being hydrophilic facilitates the interaction of polymer with water, thereby changing its

permeability and allowing water to permeate the active core in a controlled manner. This property is essential to achieve a precisely defined lag time. [55]

II. Stimuli induced pulsatile drug delivery

1. Temperature-induced pulsatile release:

2. Chemical stimuli-induced pulsatile release:

• Glucose-responsive insulin release devices

• Inflammation-induced pulsatile release

• Drug release from intelligent gels responding to antibody concentration.

• Electric stimuli-responsive pulsatile release:

1. Temperature-induced pulsatile release: [56-59]

Thermoresponsive hydrogels have been investigated as possible drug delivery carriers for stimuli responsive drug delivery systems. [56-58]. Poly (N-isopropylacrylamide) (PIPAAm) cross-linked gels have shown thermoresponsive, discontinuous swelling / deswelling phases: swelling, for example, at temperatures below 328 °C, while shrinking above this temperature. Thermoresponsive polymeric micelle systems as Kataoka et al. [59] comprehensively reviewed, the properties and biological interests of polymeric micelles make them a most noteworthy candidate as drug carrier for the treatment of cancer. The polymeric micelle is composed of amphiphilic block copolymers exhibiting a hydrophobic core with a hydrophilic corona. The application of a temperature gradient induced an on–off drug release regulation from PIPAAm PBMA micelles between 4 and 378 °C.

2. Chemical stimuli-induced pulsatile release

a) Glucose-responsive insulin release devices [60-62]

A decrease in or the absence of insulin secretion from pancreatic islets is the cause of diabetes mellitus. Diabetes mellitus patients suffer long term from a gradual decline in the efficiency of various organs, such as the occasional loss of eyesight. Several systems have already been developed which are able

to respond to glucose concentration changes. Glucose oxidase (GOD) catalyzes glucose oxidation. Utilizing this reaction, Ishihara et al. [60] prepared two types of gel membrane systems to regulate insulin permeability. They prepared and nicotinamide-immobilized gel membranes, separately.

b) Inflammation-induced pulsatile release

When human beings receive physical or chemical stress, such as injury, broken bones, etc., inflammation reactions take place at the injured sites. At the inflammatory sites, inflammation-responsive phagocytic cells, such as macrophages and polymorphonuclear cells, play a role in the healing process of the injury. During inflammation, hydroxyl radicals (OH) are produced from these inflammation-responsive cells. Yui and co-workers [61-62] used hyaluronic acid (HA), a linear mucopolysaccharide composed of repeating disaccharide subunits of *N*-acetyl-D-glucosamine and D-guluronic acid. In the body, HA is mainly degraded either by a specific enzyme, hyaluronidase, or hydroxyl 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,Yui and co-workers [61-62] prepared cross-linked HA with ethyleneglycol diglycidylether or polyglycerol polyglycidylether. These HA gels degraded only when the hydroxyl radicals were generated through the Fenton reaction between Fe^{+2} ions and hydrogen peroxide in vitro.

Thus, a surface erosion type of degradation was achieved. When microspheres were incorporated in the HA hydrogels as a model drug, these microspheres were released only when hydroxyl radicals induced HA gel degradation. The microsphere release was regulated by the surface erosion type of degradation.

c) Drug release from intelligent gels responding to antibody concentration. [63-64]

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/deswelling characteristics. Miyata and co-workers [57-58] focused on the introduction of stimuli-responsive cross-linking structures into hy-drogels. Special attention was given to antigen antibody complex formation as the cross-linking units in the gel, because specific antigen recognition of an antibody can provide the basis for a new device fabrication.

d) Electric stimuli-responsive pulsatile release: [65-67]

The combination of developments in several technologies, such as microelectronics and micromachin ing, as well as the potential need for chronotherapy, have currently assisted the development of electronically assisted drug delivery technologies. These technologies include iontophoresis, infusion pumps, and sonophoresis [65]. Several approaches have also been presented in the literature describing the preparation of electric stimuli-responsive drug delivery systems using hydrogels.

Kishi et al. [66] developed an electric stimuli induced drug release system using the electrically stimulated swelling /deswelling characteristics of polyelectrolyte hydrogels. They utilized a chemomechanical system, which contained a drug model within the polyelectrolyte gel structure. These gels exhibited reversible swelling / shrinking behavior in response to on–off switching of an electric stimulus. Thus, drug molecules within the polyelectrolyte gels might be squeezed out from the electric stimuli-induced gel contraction along with the solvent flow. To realize this mechanism, poly (sodium acrylate) microparticulate gels containing pilocarpine as a model drug were prepared.[67]

III. Externally regulated pulsatile drug delivery:

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. Magnetically regulated systems contain magnetic beads in the implant. On application of the magnetic field, drug release occurs because of magnetic beads. Saslawski et al. [68] developed different formulation for in vitro magnetically triggered delivery of insulin based on alginate spheres. In case of ultrasonically modulated systems, ultrasonic waves cause the erosion of the polymeric matrix thereby modulating drug release. Miyazaki et al [69] evaluated the effect of ultrasound (1 MHz) on the release rates of bovine insulin from ethylenevinyl alcohol copolymer matrices and reservoir-type drug delivery systems in which they found sharp drop in blood glucose levels after application of ultrasonic waves. Also irradiation with light rays the desired drug release pattern. Mathiowitzet al [70] developed photochemically controlled delivery systems prepared by interfacial polymerization of polyamide microcapsules. For this purpose, azobisisobutyronitrile (AIBN), a substance that photochemically emanates nitrogen gas, was incorporated. Due to exposure of azobisisobutyronitrile to light, causing release of nitrogen and an increase in the pressure which ruptures the capsules thereby releasing the drug.

4. RELEASE PATTERN IN PULSATILE DRUG DELIVERY SYSTEM: [24]

It is the one type of drug delivery system, where the delivery device is capable of releasing drug after predetermined timedelay (i.e. lag time) known as pulsatile drug delivery system**.** 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.
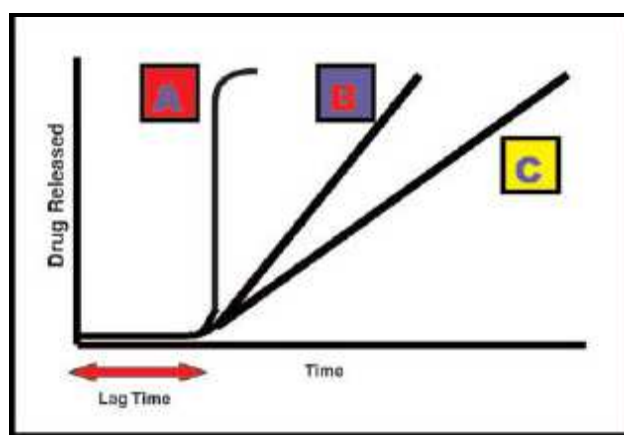

Figure 8: A = Release of drug as a "pulse" after a lag time (single pulse), B = Delivering the drug rapidly and completely after a "lag time" and C = Constant drug release over a prolonged period of time after a "lag time". [24]

5. REVIEW OF LITERATURE FOR PULSATILE DRUG DELIVERY SYSTEM:[71-82]

Table 3: Review of Literature for Pulsatile Drug Delivery System

Sr. No.	Drug	Polymer	Remarks	Reference
1	Buflomedil Hcl	spray-dried lactose, microcrystalline cellulose, croscarmellose sodium, ethylcellulose.	Spray-dried lactose and microcrystalline cellulose were coated with an inner swelling layer of croscarmellose sodium and an outer rupturable layer of ethylcellulose.The lag time of the pulsatile release tablets decreased with increasing amount of microcrystalline cellulose in the cores and increased with increasing levels of both swelling layer and rupturable ethyl-cellulose coating.	71
2	Theophylline	Ethyl-cellulose, Methocel E50,	Ethylcellulose was the best candidate polymer	72

		different disintegrants	for pulsatile release tablets	
3	Diltiazem	Ethylcellulose / Eudragit L as a coating film, polyvinylpyrrolidone	The lag time was prolonged with an increase of the coating level, whereas the drug release rate was almost constant,	73
4	Tramadol hydrochloride	Delonix regia gum (DRG) and HPMC K4M, methacrylic acid copolymers	It was observed that the lag time depends on the coating ratio of DRG to HPMC and also on press coating weight.	74
5	Diltiazem hydrochloride	hydroxypropylmethylcellulose acetate succinate (HPMCAS) and triethyl citrate (TEC), triacetin (TA), and acetyltriethy citrate (ATEC) as plasticizers	Diltiazem hydrochloride (DIL) contained in core tablets were press-coated with hydroxypropylmethylcellulose acetate succinate (HPMCAS)	75
6	Nifedipine	polyethylene oxide-polyethylene glycol mixtures	Each formulation showed a clear lag period before nifedipine release initiation, followed by sustained drug release lasting up to 24 h.	76
7	Theophylline	Eudragit	The design consists of an insoluble hard gelatin capsule body, filled with Eudragit microcapsules of theophylline and sealed with a hydrogel plug. The entire device was enteric coated, so that the variability in gastric emptying time can be overcome and a colon-specific release can be achieved.	77
8	Theophylline	glyceryl behenate, low-substituted hydroxypropylcellulose (L-HPC)	In-vivo c-scintigraphic studies were carried out for PCTs containing GB: L-HPC at 65:35 w/w and 75:25 w/w in the barrier layer in four beagle dogs, in either the fed or fasted state. The in-vivo lag time in both the fed and fasted states did not differ significantly ($p > 0.05$) from the in-vitro lag time.	78
9	Diclofenac Sodium	Calcium Pectinate	In vivo studies by gamma scintigraphy determined on rabbits showed gastroretention of beads up to 5 h. The floating beads provided expected two phase release pattern with initial lag time during floating in acidic medium followed by rapid pulse release in phosphate buffer.	79
10	Indomethacin	Eudragit S100, HPMC K100M, sodium bicarbonate	Drug containing core pellets prepared by extrusion-spheronization process, which were coated with an inner pH-dependent layer of Eudragit S100 and outer effervescent layer of sodium bicarbonate and HPMC K100M.	80
11	Aceclofenac	HPMC different grade, Eudragit	A combination of floating and pulsatile principles of drug delivery system would have the advantage that a drug can be released in distal small intestine after a defined time period of no drug release.	81
12	Meloxicam	calcium silicate, sodium alginate	Floating and pulsatile principles of drug delivery system have the advantage that a drug can be released in the upper gi tract after a definite time period of no drug release.	82

6. RECENT ADVANCES IN THE PULSATILE DRUG DELIVERY [83-84]

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. 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.

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 drug-containing core coated with an outer release-controlling 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 water-insoluble 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. Water-insoluble polymer acting as a barrier maintains the controlled release fashion like release of verapamil.

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.

7. EVALUATION TEST OF PULSATILE DRUG DELIVERY SYSTEM:

Preformulation study:[85]

Different physicochemical properties of drug and drug in excipient mass are evaluated in Preformulation study.

Drug excipients interaction study: [86]

The Fourier transform infrared (FTIR) technique and Differential scanning calorimetry (DSC) can be used to study the physical and chemical interactions between the drug and excipients used.

Evaluation of granule: [85]

Prepared granules are evaluated for Angle of Repose, Bulk Density, Tapped Density, Carrs index (or) % Compressibility, Hausner's Ratio.

Tablet Thickness:[85]

Thickness of tablet was measured using vernier caliper. Five tablets are selected randomly from individual formulations and thickness is measured using vernier caliper scale. The test is carried out in triplicate.

Uniformity of weight:[85]

Twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. Not more than two tablets deviate from the percentage given below from the average weight and none deviate by more than twice the percentage shown. The Pharmacopoieal Specification of weight variation is given in following table 4:

Table 4: Weight Uniformity Criteria for tablet

Sr. No.	Average weight of tablets (mg)	Percentage deviation
1	80 mg or less	±10
2	More than 80 mg but less than 250 mg	±7.5
3	250 mg or more	±5

Hardness/ Crushing strength:[85]

Hardness or tablet crushing strength (fc the force required to break a tablet in a diametric compression) is measured using Monsanto Hardness tester. It is expressed in Kg/cm^2. Tablets require certain amount of strength or hardness and resistance to friability, to withstand mechanical shocks of handling in manufacture, packaging, and shipping.

Evaluation of polymeric film (only in film coating approach):[86]

a) **Visual evaluation:** Casted films are visually evaluated for Physical properties of film like could be peeled off easily from the plate or not; Appearance of the film formed like smooth-rough surface, oily-non oily, Transparent-Opaque film.

b) **Tensile strength:** The casted films after drying are carefully cut into film strips (length 40 mm x width 20 mm) and investigated for tensile strength. The method used for evaluating the mechanical properties is based on guideline.

Tensile strength = Breaking Force (F)/ Cross sectional area (A)

c) **Folding endurance:** The test is carried out to check the efficiency of the plasticizer and strength of the film prepared using varying concentration of the plasticizers. The folding endurance is measured manually. A strip of film (2 x 2 cm) is cut evenly and repeatedly folded at the same place until it breaks. The number of times counted until film could be folded at the same place without breaking, this is gave the value of folding endurance. The test is carried out in triplicate.

d) **Mechanical properties:** Polymer films (6.5 X 6.7 cm2) were fixed in a self designed Teflon holder [14,23] with several holes (diameter 10 mm). Films were fixed using the holder and optionally immersed into 0.1 N HCl at 37 C for 2 h (wet films). The mechanical properties of the dry and wet films are measured with a puncture test using a Texture analyzer (n = 3). A metal probe with a hemispherical end (diameter 5 mm, length 15 cm) is driven at a speed of 5 mm/min until the film ruptured force–displacement curves are recorded and following parameters are calculated:

Puncture strength = Fmax/ ACS

Where, Fmax is the maximum applied force at film break, ACS is the cross-sectional area of the edge of the film located in the path of the cylindrical hole of the film holder, with

ACS = 2rd where r is the radius of the hole in the holder and d is the thickness of the film.

In vitro dissolution study:[87]

The in vitro dissolution study is performed using dissolution test given in monograph or in standard literature. In general case, dissolution media are 900 ml of 0.1 M HCl for 2 h (since average gastric emptying time is 2 h) and 900 ml of phosphate buffer pH 6.8 for 3 h (average small intestinal transit time). After 5 h, the dissolution medium is replaced with pH 7.4 phosphate buffer (900 ml) and tested for the drug release up to specific hour dissolution study. At the predetermined time intervals, specific volume of dissolution media (1, 2, 5, 10 ml etc..) are

withdrawn, filtered through a 0.45 µm membrane filter, diluted, and assayed at wavelength maxima using a UV spectrophotometer.

Comparison of dissolution profiles:[87]

The similarity factor (f2) given by SUPAC guidelines for a modified release dosage form is used as a basis to compare dissolution profiles. The dissolution profiles are considered to be similar when f2 is between 50 and 100. The dissolution profiles of products are compared using f2 which is calculated from the following formula:

Where n is the dissolution time and Rt and Tt are the reference) and test dissolution value at time t.

Kinetic modeling of dissolution data:[87]

The dissolution profile of all batches are fitted to various models such as zero order, first order, Higuchi, Hixon Crowell, Korsmeyer and Peppas to ascertain the kinetic of drug release.

In vivo study of prepared formulation: [87]

The prepared formulation is tested for an in vivo study to check the passage of the dosage form throughout the GIT. The purpose of the in vivo study is to find the location of the capsule during its passage through the GI tract. In this study, drug granules are replaced with barium sulfate. The dosage form is prepared in the similar manner as optimized formulation. The volunteer with overnight fasting is taken for the study. The laxative is given to the volunteer before 12 h of the study to completely empty the GIT content. The X-ray study is performed at 2-h, 3-h, 5-h, and 8-h interval.

Pharmacokinetic parameters comparision: [88]

Different pharmacokinetic parameters like Cmax (µg/ml), tmax (h), AUC (ng.h/ml), Kel (h-1) and t½ (h) are compare for optimized formulation and marketed tablet.

Anti-inflammatory activity study:[89]

Male albino rats, weighing (150 – 180 g), are used for this study; they are housed in four groups, each of 5

rats, and are allowed free access to food and water prior to the experiments.

Group I: Control untreated, received 1% carrageenan only.

Group II: Treated 1% carrageenan injection+ Optimized formulation after 2 hr.

Acute inflammation is induced in rats by the injection of 1% carrageenan solution sub-cutaneously into the sub-plantar regions of the left hind paw of rats. The thickness of the injected paw is measured immediately after carrageenan injection and after 1, 2, 3 and 4 hours using a micrometer. The mean percentage inhibition of edema thickness at each time interval is calculated from the mean increase in thickness in control and treated animals according to the equation:

Percentage inhibition in edema thickness = $[1 - (Tt/Tc)] \times 100$ (Eq. 9)

Where Tt and Tc are the mean increase in thickness of the carrageenan injected paw of the drug treated and control group respectively. The significant inhibition of inflammation indicates effectiveness of drug substance.

Dissolution−ex vivo permeation study using everted rat intestine:[90,91]

Intestine is isolated from a male Wistar rat. A median incision is made into the abdomen, the small intestine is freed, and the lumen is carefully cleared with a Krebs-Ringer solution. The intestinal segment is everted and the distal 5 cm part is used. One end of the isolated everted intestinal segment is fixed to a straight cannula and at the other end tied using a thread to a 1 g weight. The system is filled with Krebs-Ringer solution and is completely immersed into the dissolution vessel of the dissolution test apparatus containing 900 mL of suitable dissolution fluid. During the study, assemblies are maintained at $37 \pm 0.5°C$, and aeration is ensured with a continuous supply of bubbled oxygen. Marketed samples of drug and prepared optimized batch is tested (n = 3). The drug diffused from the dissolution medium (mucosal

side) into the serosal side (absorption compartment) and is analyzed by a validated analytical method at regular time intervals after filtration through a membrane filter of 0.45 μm pore size.

8. CURRENT SITUATION AND FUTURE SCOPE [92]

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. 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. [92]

9. ADVANTAGES OF PULSATILE DRUG DELIVERY SYSTEM: [93,94]

1. Extended daytime or nighttime activity
2. Reduced side effects
3. Reduced dosage frequency
4. Reduction in dose size
5. Improved patient compliance
6. Lower daily cost to patient due to fewer dosage units are required by the patient in therapy.
7. Drug adapts to suit circadian rhythms of body functions or diseases.
8. Drug targeting to specific site like colon.
9. Protection of mucosa from irritating drugs.
10. Drug loss is prevented by extensive first pass metabolism.
11. Patient comfort and compliance: Oral drug delivery is the most common and convenient for patients, and a reduction in dosing frequency enhances compliance.

10. LIMITATIONS OF PULSATILE DRUG DELIVERY SYSTEM: [94]

Pulsatile drug deleivery systems have certain limitation, so in many cases these drug delivery system is fails,

- Multiple manufacturing steps in case of Multiparticulate pulsatile drug delivery system.
- Low drug load
- Incomplete release
- In-vivo variability in single unit pulsatile drug delivery system.

11. CONCLUSION:

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.

12. REFERENCES

1) Janugade BU, Patil SS, Patil SV, Lade PD. Pulsatile drug delivery system for chronopharmacological disorders: an overview. *Journal of pharmacy research* 2009; 2 (1): 132-143.

2) Parmar RD, Parikh RK, Vidyasagar G, Patel DV, Patel CJ and Patel BD. Pulsatile Drug Delivery Systems: An Overview. *International Journal of Pharmaceutical Sciences and Nanotechnology* 2009; 2(3): 605.

3) Nitin Saigal, Sanjula Baboota, Alka Ahuja and Javed Ali. Site Specific Chronotherapeutic Drug Delivery Systems: A Patent Review. *Recent Patents on Drug Delivery & Formulation* 2009; 3: 64-70.

4) Jha N, Bapat S. Chronobiology and chronotherapeutics, *Kathmandu University Medical Journal* 2004; 2(8): 384-388.

5) Bruguolle B, Lemmer B. Recent advances in chronopharmacokinetics: methodological problems, *Life Science* 1993; 52: 1809-1824.

6) URL:http://www.uspharmacist.com/oldformat.asp?url=newlook/files/Feat/ACF2F15.cfm&pub_id, accesed on 15/9/10.

7) Botti B, Youan C. Chronopharmaceutics: Gimmick or clinically relevant approach to drug delivery. *Journal of Control Release* 2004: 337-353.

8) URL:http://thred.org/wp-content/uploads/2010/06/circadian-body-e1283009674721.jpg assessed on 1-2-2011 .

9) Myles AB, Schiller LFG, Glass D, Daly JR. Single daily dose corticosteroid treatment. *Annuals of the Rheumatoid Diseases* 1976; 35: 73-76.

10) Kowanko IC, Pownall R, Knapp MS. Time of day of prednisolone administration in rheumatoid arthritis. *Annuals of the Rheumatic Diseases* 1982; 41: 447-452.

11) Kowanko IC, Pownall R, Knapp MS. Circadian variations in the signs and symptoms of rheumatoid arthritis and in the therapeutic effectiveness of flurbiprofen at different times of the day. *British J Clin Pharma.* 1981; 11: 477-84.

12) Kowanko IC, Knapp MS, Pownall R, Swannell AJ. Domiciliary self-measurements of in rheumatoid and the demonstration of circadian rhythmicity. *Annuals of the Rheumatic Diseases* 1982; 41: 453-455.

13) Swannell AJ. Biological rhythms and their effect in the assessment of disease activity in rheumatoid arthritis. *British J Clin Practice* 1983; 38(33): 16-19.

14) Harkness JAL, Richter MB, Panayi GS. Circadian variation in disease activity in rheumatoid arthritis. *British Medical J.* 1982; 284: 551-554.

15) Huskisson EC and GP Velo ed. Chronopharmacology of anti-rheumatic drugs with special reference to indomethacin in: Inflammatory Arthropathies. *Excepta Medica* 1976: 99-105.

16) Bellamy N, Sothern RB, Campbell J. Rhythmic variations in pain perception in osteoarthritis of the knee. *Journal of Rheumatology* 1990; 17: 364-372.

17) Levi F, Le Louarn C, Reinberg A. Chronotherapy of osteoarthritis patients: optimization indomethacine sustained released (ISR). *Annual Review of Chronopharmacology* 1984; 1: 345-348.

18) Lvin M, Focan-Hensard D, Levi F. Chronobiological aspects of spondylarthritis. *Annual Review of Chronopharmacology* 1988; 5: 17-20.

19) Reinberg A, Manfredi R, Kahn MF. Tenoxicam chronotherapy of rheumatic diseases. *Annual Review of Chronopharmacology* 1990; 7: 293-296.

20) Jao F, Wong P, Huynh H, et al. Inter. Jou. Pha (1992):17

21) Percel P, Vishnupad KS, and Venkatesh GM. Timed pulsatile drug delivery systems. US Patent 6,627,2231.

22) Katstra WE, Palazzolo RD, Rowe CW, et al. Oral dosage forms fabricated by three dimensional printing. *J. Control. Rel* 2000; 66: 1-9.

23) Stevens HNE, Wilson CG, Welling PG, et al. Evaluation of pulsincap to provide regional delivery of dofetilide to the human G.I. tract. *Int. J. pharm* 2002; 236 :27-34.

24) Sharma GS, Srikanth MV, Uhumwangho MU, Phani Kumar KS and Ramana Murthy KV. Recent trends in pulsatile drug delivery systems - A review. International *Journal of Drug Delivery*, 2010; 2: 200-212.

25) Neill MC, Rashid A, Stevens HN, GB Patent No. GB2230442, 1993.

26) Sarasija S, Hota A. Colon-specific drug delivery systems. *Ind. J. Pharm. Sci.* 2002; 62(1): 1-8.

27) Kinget R, Kalala W, Vervoort L, Mooter GV. Colonic drug targeting. *J. Drug Targeting* 1998; 6(2): 129-149.

28) Krögel I, Bodmeier R. Pulsatile drug release from an insoluble capsule body controlled by an erodible plug. *Pharm. Res.* 1998; 15(3): 474-481.

29) Krögel I, Bodmeier R. Evaluation of an enzyme-containing capsular shaped pulsatile drug delivery system. Pharm. Res. 1999; 16 (9): 1424-1429.

30) Wu F, Zhang ZR, He WL, Zhang Y. Preparation and in vitro release of tetramethylpyrazine phosphate pulsincap capsule controlled by an erodible plug. Yao *Xue Xue Bao* 2002; 37(9): 733-738.

31) Crison JR., Siersma PR, Amidon GL. A novel programmable oral release technology for delivering drugs: human feasibility testing using gamma scintigraphy. *Proceed Intern Symp Control Rel. Bioact. Mater* 1996; 23: 51-52.

32) Pollock DC, Dong L, Wong P. A new system to deliver a delayed bolus of liquid drug formulation, *Proceed Intern Symp. Control. Rel. Bioact. Mater* 2001; 28: 6033.

33) Linkwitz A, Magruder JA, Merrill S. Osmotically Driven Delivery Device with Expandable Orifice for Pulsatile Delivery Effect*, US Patent No.* 5,318,558, 1994.

34) Linkwitz A., Magruder JA, Merrill S. Osmotically Driven Delivery Device with Expandable Orifice for Pulsatile Delivery Effect, *US Patent No.* 5,221,278, 1993.

35) Balaban SM, Pike JB, Smith JP, Baile CA. Osmotically Driven Delivery Devices with Pulsatile Effect, *US Patent No.* 5209746, 1993.

36) Magruder PR, Barclay B, Wong PS, Theeuwes F. Composition Comprising Salbutamol, *US Patent No.* 4751071, 1988.

37) Magruder PR, Barclay B, Wong PS, Theeuwes F. Constant Release System with Pulsed Release, *US Patent No. 4777049*, 1988.

38) Magruder PR., Barclay B, Wong PS, Theeuwes F. Composition Comprising a Therapeutic Agent and a Modulating Agent. *US Patent No. 4851229*, 1989.

39) Gazzaniga A, Iamartino P, Maffione G, Sangalli ME. Oral delayed- release system for colonic specific delivery. Int. J. Pharm. 1994; 2(108): 77-83.

40) Gazzaniga A, Sangalli ME, Giordano F. Oral chronotopic drug delivery systems: achievement of time and/or site specifity. Eur. J. Biopharm., 1994; 40(4): 246-250.

41) Gazzaniga A, Busetti C, Moro L, Crimella T, Sangalli ME, Giordano F. Evaluation of low viscosity HPMC as retarding coating material in the preparation of a time-based oral colon specific delivery system. *Proceed Intern Symp Control. Rel. Bioact. Mater* 1995; 22: 242-243.

42) Poli S, Busetti C, Moro L. Oral Pharmaceutical Composition for Specific Colon Delivery. *EP Patent No.* 0,572,942, 1993.

43) Sangalli ME, Maroni A, Zema L, Busetti C, Giordano F, Gazzaniga A. In vitro and in vivo evaluation of an oral system for time and/or site-specific drug delivery. *J. Control. Rel.* 2001; 73: 103-110.

44) Maroni A, Sangalli ME, Cerea M, Busetti C, Giordano F, Gazzaniga A. Low viscosity HPMC coating of soft and hard gelatin capsules for delayed and colonic release: preliminary investigations on process parameters and in vitro release performances. *Proceed Int. Control. Rel. Bioact. Mater* 1999; 26: 887-888.

45) Patel G. Specialized chronotherapeutic drug delivery systems, Pharmainfo.net

46) Conte U, Colombo P, Manna A, Gazzaniga A. A new ibuprofen pulsed release oral dosage form. *Drug Dev. Ind. Pharm.* 1989; 15(14- 16): 2583-2596.

47) Conte U, Manna A, Colombo P. Tablet for Pharmaceutical Use Able to Release Active Substances at Successive Times, *US Patent No.* 4,865,849, 1989.

48) Conte U, Giunchedi P, Maggi L, Sangalli ME, Gazzaniga A, Colombo P, Manna A. Ibuprofen delayed release dosage forms: a proposal for the preparation of an in vitro/in vivo pulsatile system, *Eur. J. Pharm.* 1992; 38(6): 209-212.

49) Krögel I, Bodmeier R. Floating or pulsatile drug delivery systems based on coated effervescent cores. *Int. J. Pharm* 1999*;* 187: 175-184.

50) Ueda Y, Hata T, Yamaguchi H, Ueda S, Kotani M. Time Controlled Explosion System and Process for Preparation for the Same, *US Patent No.* 4,871,549, 1989.

51) Ueda Y, Hata T, Yamaguchi H, Kotani M, Ueda S. Development of a novel drug release system, time-controlled explosion system (TES), Part 1: concept and design. *J. Drug Targeting* 1994; 2: 35-44.

52) Ueda S, Yamaguchi H, Kotani M, Kimura S, Tokunaga Y, Kagayama A, Hata T. Development of a novel drug release system, time-controlled explosion system (TES), Part II: design of multiparticulate TES and in vitro drug release properties. *Chem. Pharm. Bull.* 1994; 42(2): 359-363.

53) Amidon GL, Leesman GD. Pulsatile Drug Delivery System, *US Patent No.* 5,229,131, 1993.

54) Bodmeier R, Guo X, Sarabia RE, Skultety P. The influence of buffer species and strength on diltiazem HCl release from beads coated with aqueous cationic polymer dispersions, Eudragit RS, RL 30D, *Pharm. Res.,* 1996; 13 (1): 52-56.

55) Beckert TE, Pogarell K, Hack I, Petereit HU. Pulsed drug release with film coatings of Eudragit & Mac226; RS 30D. *Proceed Int'l Symp Control. Rel. Bioact. Mater* 1999; 26: 533- 534.

56) T. Okano, N. Yui, M. Yokoyama, R. Yoshida. Advances in Polymeric Systems for Drug Delivery, Gordon and Breach, Yverdon, Switzerland, 1994.

57) Y.H. Bae, T. Okano, S.W. Kim. 'On–off' thermocontrol of solute transport. I. Temperature dependence of swelling of *N*-isopropylacrylamide networks modified with hydrophobic components in water, *Pharm. Res.* 1991; 8 (4): 531–537.

58) Y.H. Bae, T. Okano, S.W. Kim. 'On–off' thermocontrol of solute transport. II. Solute release from thermosensitive hydrogels, Pharm. Res. 1991; 8 (5): 624–628.

59) K. Kataoka, A. Harada, Y. Nagasaki. Block copolymer micelles for drug delivery: design, characterization and biological significance. *Adv. Drug Deliv. Rev.* 2001; 47: 113–131.

60) K. Ishihara, M. Kobayashi, I. Shinohara. Control of insulin permeation through a polymer membrane with responsive function for glucose, Makromol. *Chem. Rapid Commun.* 1983; 4: 327–331.

61) N. Yui, T. Okano, Y. Sakurai. Inflammation responsive degradation of crosslinked hyaluronic acid gels. J. Control. Release 1992; 22: 105–116.

62) N. Yui, J. Nihira, T. Okano, Y. Sakurai. Regulated release of drug microspheres from inflammation responsive degradable matrices of crosslinked hyaluronic acid. *J. Control. Release 1*993; 25: 133–143.

63) T. Miyata, N. Asami, T. Uragami. A reversibly antigen responsive hydrogel. *Nature* 1999; 399: 766–769.

64) T. Miyata, N. Asami, T. Uragami. Preparation of an antigen sensitive hydrogel using antigen–antibody bindings, *Macro molecules* 1999; 32: 2082–2084.

65) B. Berner, S.M. Dinh. Electronically assisted drug delivery: an overview, in: B. Berner, S.M. Dinh (Eds.), *Electronically Controlled Drug Delivery* 1998: 3–7.

66) R. Kishi, M. Hara, K. Sawahata, Y. Osada. Conversion of chemical into mechanical energy by synthetic polymer gels (chemomechanical system). *Polymer Gels — Fundamentals and Biomedical Applications,* Plenum Press, New York, 1991, pp. 205–220.

67) I.C. Kwon, Y.H. Bae, T. Okano, B. Berner, S.W. Kim. Stimuli sensitive polymers for drug delivery systems, *Makro mol. Chem. Macromol. Symp* 1990; 33: 265–277.

68) Saslawski O, Weigarten C, Benoit JP, et al. Magnetically responsive microspheres for the pulsed delivery of insulin. *Life Sci.* 1988; 42 (16): 1521-1528.

69) Miyazaki S, Yokouchi C and Takada M. External control of drug release: controlled release of insulin from a hydrophilic polymer implant by ultrasound irradiation in diabetic rats. *J. Pharm. Pharmacol* 1988; 40: 716-717.

70) Mathiowitz E, Raziel A, Cohen MD, et al. Novel deciccants Based on Designed Polymeric Blends. *J. Appl.Polym. Sci.* 1981; 26: 809-822.

71) Sungthongjeen S, Puttipipatkhachorn S and Dashevsky A. Development of pulsatile release tablets with swelling and rupturable layers. *Journal of Controlled Release* 2004; 95: 147–159.

72) Zhu Y, and Zheng L. Development and mathematical simulation of theophylline pulsatile release tablets. *Drug Dev. Ind. Pharm.* 2005; 31(10): 1009-1017.

73) Fan TY, Wei SL, Yan WW and Li J. An investigation of pulsatile release tablets with ethylcellulose and Eudragit L as film coating materials and cross-linked polyvinyl pyrrolidone in the core tablets. *Journal of Controlled Release* 2001; 77: 245–251.

74) Dabhi C, Randale S, Belgamwar V and Gattani S. Predictable pulsatile release of tramadol hydrochloride for chronotherapeutics of arthritis. *Drug Delivery* 2010; 17(5): 273–281.

75) Fukui E, Miyamura N, Yoneyama T and Kobayashi M. Drug release from and mechanical properties of press-coated tablets with hydroxypropylmethylcellulose acetate succinate and plasticizers in the outer shell, *International Journal of Pharmaceutics* 2001; 217: 33–43.

76) Sawada T, Kondo H, Nakashima H. Time-release compression-coated core tablet containing nifedipine for chronopharmacotherapy. *International Journal of Pharmaceutics* 2004; 280: 103–111.

77) Mastiholimath V, Dandagi P and Jain S. Time and pH dependent colon specific, pulsatile delivery of theophylline for nocturnal asthma. *International Journal of Pharmaceutics* 2007; 328: 49–56.

78) Ghimire M, McInnes F and Watson D. In-vitro/in-vivo correlation of pulsatile drug release from press-coated tablet formulations: A pharmacoscintigraphic study in the beagle dog. *European Journal of Pharmaceutics and Biopharmaceutics* 2007; 67: 515–523.

79) Badve S, Sher P and Korde A. Development of hollow/porous calcium pectinate beads for floating-pulsatile drug delivery. *European Journal of Pharmaceutics and Biopharmaceutics* 2007; 65: 85–93.

80) Jessy S and Patole V. Novel Floating Pulsatile Approach for Chronotherapeutic Release of Indomethacin, *Dhaka Univ. J Pharm. Sci.* 2007; 6(1): 37-41.

81) Patole V, Shaji J and Lodha S. Development of floating pulsatile drug delivery for sequential Release of aceclofenac, KM Kundnani college of pharmacy, Mumbai academic project.

82) Sharma S and Pawar A. Low density multiparticulate system for pulsatile release of meloxicam. *International Journal of Pharmaceutics* 2006; 313: 150–158.

83) Dashevsky A and Mohamad A. *Int. J. pharm.* 2006; 318: 124-131.

84) Sharma S and Pawar A. Low Density multiparticulate system for pulsatile release of meloxicam. *Int. J. pharm.* 2006; 313(1): 150-158.

85) Lachman "The theory and Practice of Industrial Pharmacy" 3rd edition.

86) Ahmad Mohamad, Andrei Dashevsky. pH-independent pulsatile drug delivery system based on hard gelatin capsules and coated with aqueous dispersion Aquacoat ECD. *European Journal of Pharmaceutics and Biopharmaceutics* 2006; 64: 173-179.

87) Dasharath M Patel, Rushiraj H Jani, Chhagan N Patel. Design and evaluation of colon targeted modified pulsincap delivery of 5-fluorouracil according to circadian rhythm. *International Journal of Pharmaceutical Investigation* 2011; 1(3): 172-181.

88) Santanu Ghosh, BB Barik. A comparative study of the pharmacokinetics of conventional and sustained-release tablet formulations of aceclofenac

in healthy male subjects, *Tropical Journal of Pharmaceutical Researc*h 2010; 9 (4): 395-399.

89) Maha Abd El-Hamid Marzouk, Alaa El-Din Ali Kassem, Ahmed Mahmoud Samy, Riham Ibrahim Amer. In-vitro release, Thermodynamics and Pharmacodynamic Studies of Aceclofenac Transdermal Eudragit Patches. *Drug Invention Today* 2009; 1(1): 16-22.

90) Kale VV, Kasliwal RH, Avari JG. Attempt to design continuous dissolution-absorption system using everted intestine segment for in vitro absorption studies of slow drug release formulations. *Dissolution Technologies* 2007; 14: 31–36.

91) Mariappan TT, Singh S. Evidence of efflux-mediated and saturable absorption of rifampicin in rat intestine using the ligated loop and everted gut sac techniques. *Mol Pharm.* 2004; 1: 363–367.

92) Asim Sattwa Mandal, Nikhil Biswas, Kazi Masud Karim, Arijit Guha, Sugata Chatterjee, Mamata Behera, Ketousetuo Kuotsu. Drug delivery system based on chronobiology—A review. *Journal of Controlled Release* 2010; 10.

93) Sunil kamboj, G D Gupta, Jagmohan Oberoy. Matrix Tablets : An Important Tool for Oral Controlled-Release Dosage Forms, *Pharmainfo net* 2009; 7(6): 1-9.

94) Rathod Shruti. Colon Targeted Pulsatile Drug Delivery : A Review 2007; 5(2): 1-11.