

**PULSATILE DRUG DELIVERY SYSTEM: A REVIEW****Neha P. Singh*, G. Ganarajan and Preeti Kothiyal**

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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. These

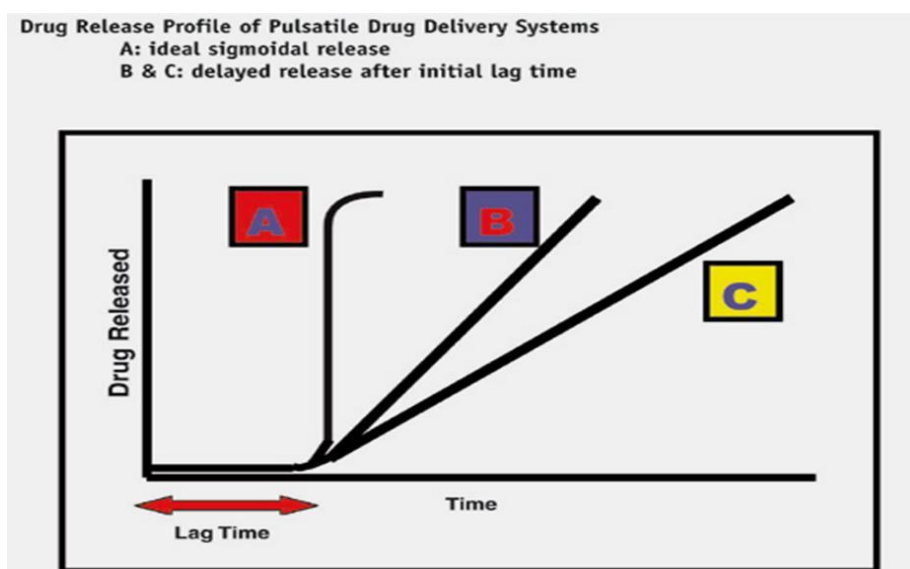
systems are beneficial for the drugs having chronopharmacological behavior such as drug used in treatment of rheumatoid arthritis, osteo arthritis and ankylosing spondylitis like inflammatory disorders. Current review article discussed the reasons for development of pulsatile drug delivery system, types of the disease in which pulsatile release is required, classification, advantages, and limitation, of pulsatile drug delivery system.

KEYWORDS: These systems are designed according to the biological rhythm of the body.

INTRODUCTION

Pulsatile drug delivery systems are time-controlled drug delivery system. These systems are design to achieve time specific and site specific delivery of drugs according to the circadian rhythm of the body. Pulsatile release pattern has gained most popular form of controlled drug delivery system because conventional systems with a continuous release are not ideal. Pulsatile systems are beneficial for the drugs having chronopharmacological behavior. The

principle rationale for the use of pulsatile release is for the drugs where a constant drug release, i.e., a zero-order release is not desired. The release of the drug as a pulse after a lag time (an interval of no drug release) has to be designed in such a way that a complete and rapid drug release follows the lag time. In chronopharmacotherapy (timed drug therapy) drug administration is synchronized with biological rhythms to produce maximal therapeutic effect and minimum harm for the patient. Pulsatile release is also useful for the targeting of the drug irritating the stomach or degradable therein, as well for drugs developing biological tolerance or with an extensive first pass metabolism.



Drug release profile of pulsatile drug delivery systems

Targets for pulsatile drug delivery

Disease	Chronological behaviour	Drugs used
Asthma	Precipitation of attacks during night or at early morning	Antihistamines, B2 agonist
Attention deficit syndrome	Increase in DOPA level in afternoon.	Methylphenidate
Arthritis	Pain increases in early morning caused by the marked release of inflammatory cytokines, including interleukin-6 in the early hours of the morning.	NSAIDs, Glucocorticoids
Cancer	Blood flow to tumour is threefold greater during each daily activity phase of the circadian cycle than during the daily rest phase	Vinca alkaloids, Taxans
Duodenal ulcers	Gastric acid secretion is highest at night, bowel motility&	Proton pump inhibitors

	gastric emptying are slower at night	
Peptic ulcers	Acid secretion is high in afternoon & at night	H2 Blockers
Hypercholesterolemia	Cholesterol synthesis is generally higher during night than day time	HMG CoA reductase inhibitor
Diabetes mellitus	Increase in blood sugar level after meal	Sulfonylurea, Insulin
Neurological disorder	Central pathophysiology of epilepsy and behavioural classification of convulsive events	MAO-B inhibitor
Cardiovascular disease	BP is at its lowest during sleep cycle.	Nitro-glycerine, CCBs, ACE inhibitors

NECESSITY OF PULSATILE DRUG DELIVERY SYSTEMS

There are many conditions and diseases where sustained release formulations do not show good efficacy. In such cases Pulsatile DDS is applicable.

1. First pass metabolism

Some drugs, such as beta blockers, and salicylamide, undergo extensive first pass Metabolism and require fast drug input to saturate metabolizing enzymes in order to minimize pre-systemic metabolism. Thus, a constant/sustained oral method of delivery would result in reduced oral bioavailability⁹.

2. Biological tolerance

Drug plasma profiles are often accompanied by a decline in the pharmacotherapeutic effect of the drug, e.g., biological tolerance of transdermal nitroglycerin, salbutamol sulphate.

3. Special chronopharmacological needs

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

4. Local therapeutic need

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

5. Gastric irritation or drug instability in gastric fluid

Protection from gastric environment is essential for the drugs that undergo degradation in gastric acidic medium (e.g.: peptide drugs), irritate the gastric mucosa (NSAIDS) or induce nausea and vomiting.

Advantages of the Pulsatile drug delivery systems:

1. These systems can be used for extended day time or night time activity.
2. They reduce the dose frequency, dose size and cost, which ultimately reduce side effects, thereby improving patient compliance.
3. Hormones such as renin, aldosterone, and cortisol etc. their levels in blood may alter with circadian rhythms therefore drug delivery through this system suits circadian rhythms of body functions or diseases.
4. Drug targeting to a specific site, like the colon (in case of ulcerative colitis) can be achieved.
5. This system helps to prevent the continuous presence of some drugs (e.g. salbutamol sulphate) that produce biological tolerance and thus they increase their therapeutic effect.
6. These systems are beneficial for the drugs having chronopharmacological behavior where night time dosing is required and for the drugs having high firstpass effect.
7. They provide constant drug levels at the site of action and prevent the peak-valley fluctuations.
8. Protection from gastric environment is essential for drugs that cause gastric irritation (e.g. NSAIDS) or get degraded in gastric medium (e.g. peptide drugs) so enteric coated Pulsatile drug delivery system can be the best option for it.

Limitations

1. Multiple manufacturing steps in case of Multiparticulate drug delivery system.
2. Low drug loading capacity and incomplete release of drug.
3. In vivo variability in single unit pulsatile drug delivery system.
4. Drug dose manipulation in case of child and elder patients is not possible.
5. Immediate withdrawal of drug is not possible.

Classification

Methodologies for the PDDS can be broadly classified into four classes;

I. Time controlled pulsatile release

- A. Single unit system
- B. Multi-particulate system

II. Stimuli induced

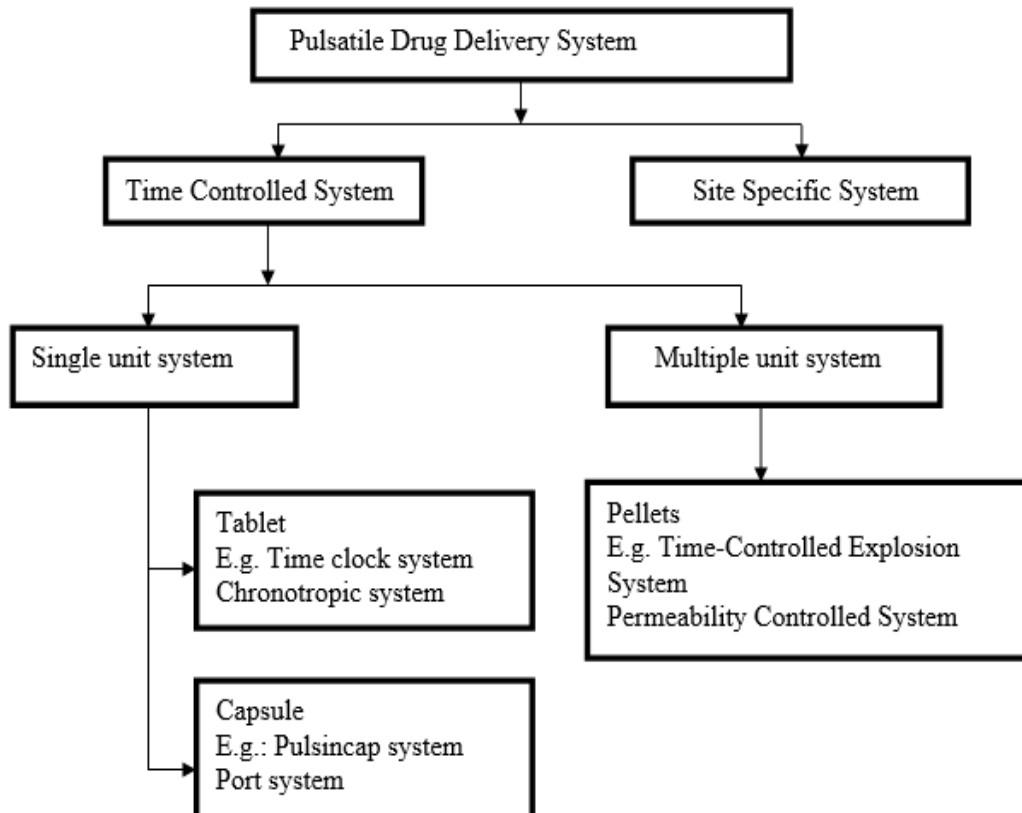
- A. Inflammation-induced Pulsatile Release
- B. Temperature induced systems
- C. pH Sensitive Drug Delivery System

III. Chemical stimuli induced pulsatile systems

- A. Glucose-responsive Insulin Release Devices
- B. Drug release from intelligent gels responding to antibody concentration

IV. External stimuli pulsatile release

- A. Micro Electro Mechanical Systems (MEMS)
- B. Electro responsive pulsatile release
- C. Magnetically induced pulsatile release

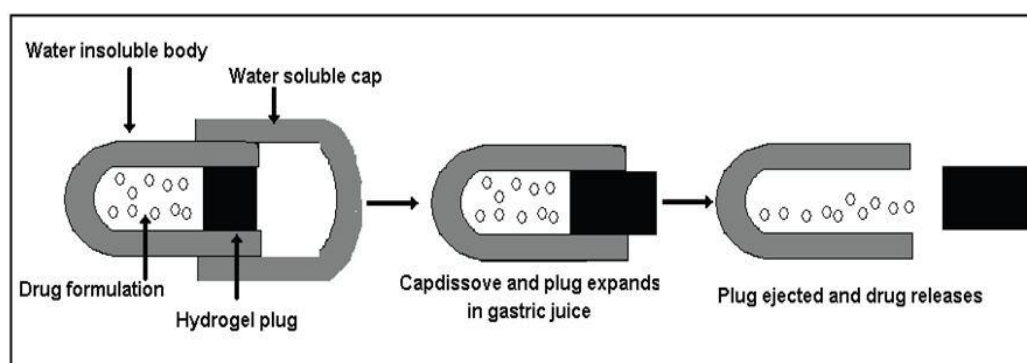


Classification of pulsatile drug delivery system.

I : Time controlled Pulsatile release system

These time-controlled systems can be classified as single unit (e.g., tablet or capsule) or multiple unit systems.

A. Single Unit System Capsular Systems : Different single unit capsular PDDS have been developed. A general design of such systems consists of an insoluble capsule body housing a drug and a plug. The plug is removed after a predetermined time lag due to swelling, erosion, or dissolution.



The Pulsincap system is an example of such a system that is made up of a water-insoluble capsule body filled with drug formulation. The body is closed at the open end with a swellable hydrogel plug. Upon contact with dissolution medium or gastro-intestinal fluids, the plug swells, pushing itself out of the capsule after a time lag. This is followed by a spontaneous release of the drug. The time lag can be controlled by manipulating the dimension and the position of the plug. The plug material consists of insoluble but permeable and swellable polymers e.g.: polymethacrylates, erodible compressed polymers (e.g: hydroxypropylmethyl cellulose, polyvinyl alcohol, polyethylene oxide), congealed melted polymers (e.g: saturated polyglycolated glycerides, glycerylmonoole and enzymatically controlled erodible polymer e.g: pectin. However, there was a potential problem of variable gastric residence time, which was overcome by enteric coating the system to allow its dissolution only in the higher pH region of small intestine.

Pulsatile System Based On Osmosis

- **Port Systems:** This system consists of a gelatin capsule coated with a semi permeable membrane (e.g: cellulose acetate) housing an insoluble plug (e.g: lipidic) and an osmotically active agent along with the drug formulation. When it comes in contact with the aqueous medium, water diffuses across the semi permeable membrane, resulting in increased inner

pressure that ejects the plug after lag time. The time lag is controlled by the thickness of semi permeable membrane. In order to deliver drug in liquid form, an osmotically driven capsular system was developed. In this system, liquid drug is absorbed into highly porous particles, which release the drug through an orifice of a semi permeable capsule supported by an expanding osmotic layer after the barrier layer is dissolved.

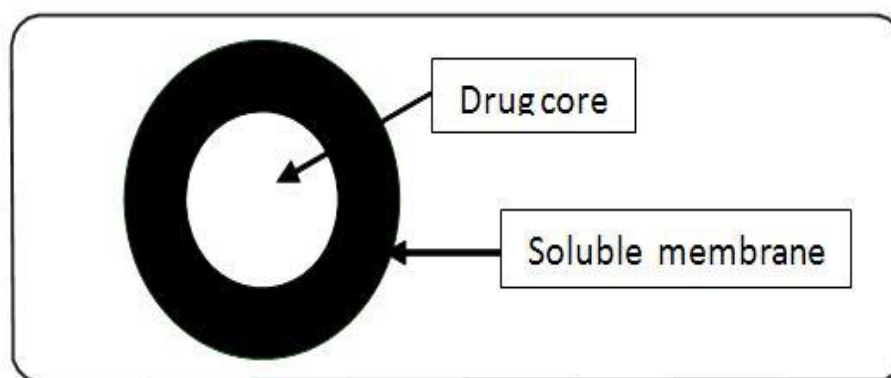
- **Delivery by a Series of Stops:** This system is described for implantable capsules. The osmotically driven delivery capsule contains therapeutically active agent and water-absorptive osmotic engine separated by a slider partition to deliver the drug in a pulsatile manner through the orifice. The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

- **Single Unit Systems Delivery by Solubility Modulation:** These systems contain a solubility modulator for pulsed delivery of variety of drugs. The system was developed for delivery of salbutamol sulphate. The compositions contain the drug (salbutamol sulphate) and a modulating agent, sodium chloride (NaCl). The amount of NaCl was such that it was less than the amount needed to maintain saturation in a fluid that enters the osmotic device. The pulsed delivery is based on drug solubility. The modulating agent can be a solid organic acid, inorganic salt, or organic salt.

- **A System Based on Expandable Orifice:** This device is in the form of capsule from which the drug is delivered by the capsule's osmotic infusion of moisture from the body. There is an orifice consisting of elastic material on the capsule's wall. It is so small that under relaxed condition flow of the drug through the orifice is nearly zero. When the pressure is developed inside the shell elastic wall is stretched. Consequently the orifice expands sufficiently from time to time to allow the release of drug in pulsatile manner.

Delivery by Reservoir Systems with Erodible or Soluble Barrier Coatings: In such systems the drug release is controlled by the dissolution or erosion of the outer coat which is applied on the core containing drug. Time dependent release of the active ingredient can be obtained by optimizing the thickness of the outer.

These systems are another class of reservoir type pulsatile systems with a barrier layer, which dissolves or erodes after a specific lag time followed by burst release of drug from the reservoir core. Generally in these, the lag time is controlled by thickness of coating layer. For instance, a chronotropic system which consists of a drug containing core layered with HPMC and a top layer of enteric coating, the lag time before drug release will be dependent upon the thickness and viscosity grade of HPMC layer. Since drug release mechanism in these types of systems is dissolution, that's why, a high degree of drug solubility relative to dose of drug is essential for rapid release of drug after the lag period.



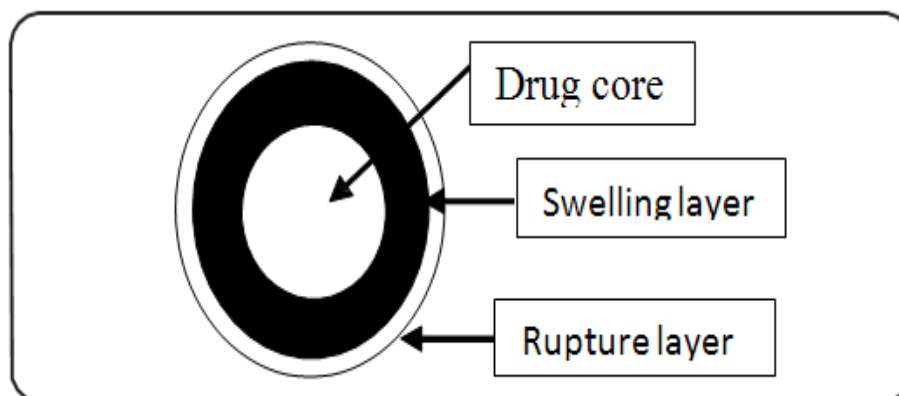
Delivery System with Soluble or Erodible Membranes

B) Multiparticulate Systems: Multiparticulate systems are reservoir type of devices with a coating, which either ruptures or changes its permeability. Drug is coated over sugar seeds these granules may then be packaged in a capsule or compressed with additional excipients to form a tablet. The active pharmaceutical ingredient may also be blended or granulated with polymers before coating to provide an additional level of control. However, drug loading in this type of system is low due to higher need of excipients.

Pulsatile Delivery by Change in Membrane Permeability: These systems are designed when a sigmoidal release pattern is desired, therapeutically beneficial for timed release and colonic drug delivery. Drug release is achieved by change in permeability of polymeric coating layer in presence of certain counter ions of surrounding media, based on this Narisawa et al, developed a device capable of pulse-release depending on the change in diffusion properties of Eudragit RS.

The release profile of systems based on permeability changes depend strongly on physicochemical properties of the drug and its interaction with membrane. Therefore, with

this system a pulsatile release profile may be obtained for some particular drug molecules in a specific form but cannot be generally applied to all drugs.



Delivery System with Repturable Coating

II. Stimuli induced pulsatile release system

A. Inflammation-induced Pulsatile Release: Inflammation takes place at the injured sites. During inflammation, hydroxyl radicals are produced from these inflammation-responsive cells. Yui and co-workers focused on the inflammatory induced hydroxyl radicals and designed drug delivery systems, which responded to the hydroxyl radicals and degraded in a limited manner. They used hyaluronic acid (HA) which is specifically degraded by the hyaluronidase or free radicals. Degradation of HA via the hyaluronidase is very low in a normal state of health. Degradation via hydroxyl radicals however, is usually dominant and rapid when H₂O₂ is injected at inflammatory sites. Thus, it is possible to treat patients with inflammatory diseases like rheumatoid arthritis; using anti-inflammatory drug incorporated HA gels as new implantable drug delivery systems.

B. Temperature induced systems: Thermo-responsive hydrogel systems have been developed for pulsatile release. In these systems the polymer undergoes swelling or deswelling phase in response to the temperature which modulate drug release in swollen state. Y.H. Bae et al developed indomethacin pulsatile release pattern in the temperature ranges between 20°C and 30°C by using reversible swelling properties of copolymers of N-isopropylacrylamide and butyrylacrylamide.

C. pH Sensitive Drug Delivery System: Such type of pulsatile drug delivery system contains two components one is of immediate release type and other one is pulsed release which releases the drug in response to change in pH. In case of pH dependent system

advantage has been taken of the fact that there exists different pH environment at different parts of the gastrointestinal tract. By selecting the pH dependent polymers drug release at specific location can be obtained. Examples of pH dependent polymers include cellulose acetate phthalate, polyacrylates, sodium carboxy methylcellulose, Eudragit E-100.

III. Chemical stimuli induced pulsatile systems

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

A. Glucose-responsive Insulin Release Devices

There has been much interest in the development of stimuli-sensitive delivery system that releases therapeutic agents in presence of specific enzyme or protein. In these systems there is release of the drug after stimulation by any biological factor like enzyme, pH or any other chemical stimuli. This novel type of glyco-sensitive gel may have potential utilities in self-regulated drug-releasing systems as well as in other applications such as actuators, regulators, and separation systems with glyco-sensitivity. The fabrication of insulin delivery systems for the treatment of diabetic patients. Delivering insulin is different from delivering other drugs, since insulin has to be delivered in an exact amount at the exact time of need. Many devices have been developed for this purpose and all of them have a glucose sensor built into the system. This enzyme is probably the most widely used in glucose sensing, and makes possible to apply different types of pH- sensitive hydrogels for modulated insulin delivery. This pH change induces swelling of the polymer which results in insulin release. Insulin by virtue of its action reduces blood glucose level and consequently gluconic acid level also gets decreased and system turns to the deswelling mode thereby decreasing the insulin release.

B. Drug release from intelligent gels responding to antibody concentration

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

IV. External stimuli Pulsatile release

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

A. Micro Electro Mechanical Systems (MEMS)

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

B. Magnetically Induced Pulsatile Release.

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

C. Electro Responsive Pulsatile Release

The combination of developments in several technologies, such as microelectronics and micromachining, 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. 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.

CONCLUSIONS

It can be concluded that pulsatile drug delivery systems offer a key for delivery of drugs exhibiting chronopharmacological behavior, necessity of night time dosing, etc. 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 pathophysiology, for which, pulsatile drug delivery is beneficial. The drug is delivering in this system when its actual concentration is needed as per chronological need, so pulsatile release systems should be promising in the future.

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