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Pulsatile Drug Delivery System: An Overview

Vaibhav Gadade[1*], Ashok Gadade[1], Dhanvantari Shivarkar[2], Tushar Katariya[2]

1. Anand Charitable Santha, College of Pharmacy, Ashti, Beed, Maharashtra, India
   [E-mail: vaibhavjgadade@gmail.com]
2. Pravara Rural College of Pharmacy, Pravaranagar, Ahemadnagar, Maharashtra, India.
3. Shri Amolak Jain Vidya Prasarak Mandal's Pharmacy College, Kada, Beed, Maharashtra, India.

Current research in the field of drug delivery devices, pulsatile drug delivery systems (PDDS) are gaining importance, as these systems deliver the drug at specific time as per the pathophysiological need of the disease, resulting in improved patient therapeutic efficacy and compliance. Diseases wherein pulsatile drug delivery systems are promising include asthma, peptic ulcer, cardiovascular diseases, arthritis, attention deficit syndrome in children, and hypercholesterolemia. These systems are beneficial for the drugs having chronopharmacological behavior where night time dosing is required and for the drug having high first pass metabolism effect and having specific site of absorption in gastrointestinal tract. In pursuit of pulsatile release, various design strategies have been proposed, mainly including time controlling, stimuli induced and externally regulated formulations. In this article, an attempt has been made to discuss several types of drug delivery systems developed by various researchers that show pulsatile drug delivery characteristics.

Keyword: PDDS, Lag Time, Time Controlling Systems, Stimuli Induce

1. Introduction

With the advancement of the technologies in the pharmaceutical field, drug delivery systems have drawn an increasing interest over the last few decades. Nowadays, the emphasis of pharmaceutical galenic research is turned towards the development of more efficacious drug delivery systems with already existing molecule rather going for new drug discovery because of the inherent hurdles posed in drug discovery and development process[1].

Worldwide several researches are going on for the development of new drug delivery system. In conventional therapy drug is released immediately after medication. So, the drug concentration in the plasma is raised and sometimes it is more than the toxic level. The target of drug discovery is to obtain maximum drug efficacy and minimum side effect. With the advancement of technologies in the pharmaceutical field drug therapy has changed its path. Although sustained and constant release systems have been developed biological systems are not so responsive to these release systems. In addition, sustained and controlled release devices are not applicable in some cases like time-programmed administration of hormones and many drugs. Those hormones and drugs can also easily be degraded by metabolic enzymes and resistance may be developed. The living systems are predictable dynamic resonating systems which require different amounts of drug at expected times within the circadian cycle[2]. It is not a surprise that all bodily functions from the

single cell to the genome are organized and synchronized in time [3].

Pulsatile drug delivery system has fulfilled this requirement. Pulsatile drug release is such a system where drug is released suddenly after well-defined lag time or time gap according to circadian rhythm of disease states. No drug is released from the device within this lag time [4].

This review focuses on recent developments by various researchers in pulsatile delivery systems. As already mentioned, these systems can be classified either according to their target release profile (i.e. time or site specific) or according to the technology used (i.e. single unit or multi-unit). The contents of each group are further divided to several subgroups. The majority of the systems discussed in each paragraph are only indicative, as each invention in reality belongs to more than one subgroup.

2. Chronopharmaceutics

'Chronopharmaceutics' consist of two words; Chronobiology and Pharmaceutics. Chronobiology is the study of biological rhythms and their mechanism[4]. Biological rhythms are defined by a number of characteristiccs[5]. There are three types of mechanical rhythms in our body; namely, Circadian rhythm word originates from Latin word 'circa' means about and 'dies' means day[6], Ultradian rhythm means oscillation of shorter duration (more than one cycle per 24 h) and Infradian rhythm having oscillations longer than 24 h (less than one cycle per day). Circadian rhythm regulates many body functions in humans like metabolism, physiological behavior, sleep pattern, hormone production etc.[2]

- **Period:** Period is the duration of time required to complete a single cycle.
- **Level:** Level is the baseline around which rhythmic variation occurs.
- **Amplitude:** Amplitude is a measure of the magnitude of the predictable-in time variability due specifically to a biological rhythm.
- **Phase:** Phase refers to the clocking of specific features, such as the peak and trough values, of a rhythm relative to the corresponding time scale.

3. Diseases with Established Circadian Rhythms

Diseases with established circadian rhythms include asthma, arthritis, duodenal ulcer, cancer, cardiovascular diseases, diabetes, hypercholesterolemia, neurological disorders etc.

3.1 Allergic Rhinitis

Common symptoms of allergic rhinitis are sneezing, nasal rhinorrhea, red itchy eyes, nasal pruritus and nasal congestion. Symptoms of the Allergic rhinitis found to occur most frequently before breakfast and in the morning and least frequently in the middle of the day. There are two phases of occurrence of allergic rhinitis i.e. early phase (developing within minutes) and late phase (manifesting after 12–16 h). The early phase happens due to release of histamine, prostaglandins, cytokines, TNF-α, chemotactic factors etc. resulting in sneezing, nasal itch, rhinorrhea. On the other hand late phase is shown due to elaboration, adhesion and infiltration of circulating leukocytes, T cells and eosinophils evoking nasal congestion, obstruction due to the exacerbation of inflammation of the nasal, sinus and other tissue of the upper airway [5].

3.2 Alzheimer's Disease

Change of circadian rhythm is also seen in patients with Alzheimer's disease. Individuals with Alzheimer's show less diurnal motor activity, a higher percentage of nocturnal activity, lower inter daily stability of motor activity, and a later activity acrophase (time of peak) than normal healthy individuals[7].

3.3 Bronchial Asthma

Airway resistance increases progressively at night in asthmatic patient. It is characterized by airway inflammation resulting in hyper responsiveness of lower respiratory tract to various environmental stimuli. It is a good target for chronotherapy because bronchoconstriction and exacerbation of symptoms vary on circadian fashion [8,9].

3.4 Cancer

There are many clock genes involved in transcriptional and post-transcriptional activation

and inhibition of regulatory loops that produce circadian oscillation in mammalian cells. The rhythmic circadian changes in tumor blood flow and cancer growth are relevant both when tumors are small and growing most rapidly and when they are larger and growing more slowly. The blood flow to tumors and tumor growth rate are each up to threefold greater during each daily activity phase of the circadian cycle than during the daily rest phase[10].

3.5 Cardiovascular Diseases

Several functions (e.g. BP, heart rate, stroke volume, cardiac output, blood flow) of the cardiovascular system are subject to circadian rhythms. For instance, capillary resistance and vascular reactivity are higher in the morning and decrease later in the day. Platelet agreeability is increased and fibrinolytic activity is decreased in the morning, leading to a state of relative hypercoagulability of the blood. Cardiac events also occur with a circadian pattern[11].

3.6 Diabetes

Insulin is released in pulsatile fashion but sometimes it is irregular. Insulin can show cyclic rhythmicity of 8–30 min[12].

3.7 Duodenal ulcer

Generally gastric acid secretion is highest in the evening in duodenal ulcer patients and decreases in the early morning [13,14].

3.8 Hypercholesterolemia

A circadian rhythm takes place during cholesterol synthesis. Cholesterol synthesis is generally higher during night time than day light. Sometimes it varies according to individuals. The maximal production occurs early in the morning, i.e., 12 h after last meal[15].

3.9 Infectious diseases

The elevation of body temperature, fever due to bacterial infections is higher in the evening while that due to viral infections is more likely in the morning[16].

3.10 Pain

In arthritis there is circadian rhythm in the plasma concentration of C-reactive protein and interleukin-6 of patient with rheumatoid arthritis. Patients with osteoarthritis tend to have less pain in the morning and more at night. While patients with rheumatoid arthritis have pain that usually peaks in the morning and decreases throughout day. Aspirin, paracetamol, NSAIDs and morphinomimetics are indicated against nociceptive pain, while anticonvulsants, tricyclic antidepressants and local anesthetics are used against neurogenic pain[17].

3.11 Parkinson's Disease

Autonomic dysfunction seen in Parkinson's disease discloses many alterations in circadian rhythm of blood pressure, amplified diurnal blood pressure variability and postprandial hypotension. But existence of circadian rhythm in this disease has not been evaluated. Clinical data shows daily fluctuations of motor activity pattern but the effect of the phase of the disease and the subsequent roles of drugs are difficult to estimate[18].

3.12 Coagulation Disorder And Thrombosis

Circadian rhythm has been found in many components of circulatory and haemostatic systems such as muscle cells, aorta, peripheral vascular muscle and endothelium. Alterations in the time structure of circadian rhythms may lead to hypercoagulability and thrombosis or hypocoagulabity and hemorrhage [19].

4. Pulsatile Drug Delivery System (Pdds)

PDDS is defined as the rapid and transient release of certain amount of drug molecules within a short time period immediately after a pre-determined off-release period, i.e. lag time[4]. After the lag phase, pulsatile delivery systems may give rise to a prompt and quantitative, repeated or prolonged release pattern depending on their formulation characteristics which is shown in Figure 1.

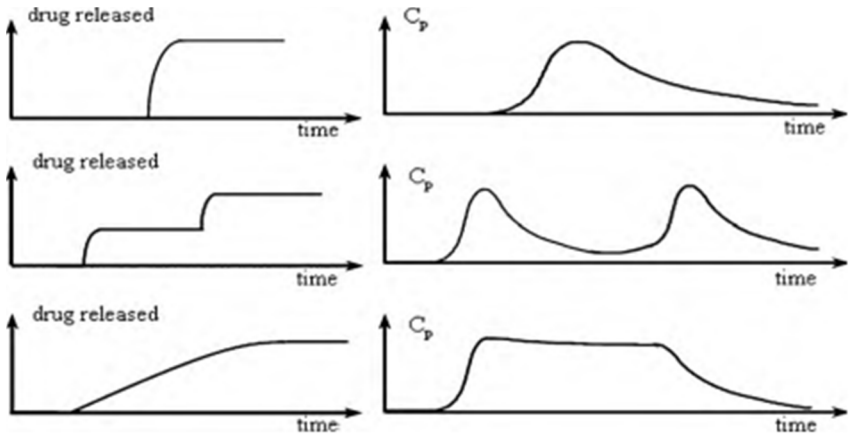

Figure1. Drug Release Pattern from PDDS

Lag time is defined as the time between when a dosage form is placed into an aqueous environment and the time at which the active ingredient begins to get released from the dosage form. While not meant to be limiting, one way to measure lag time is to determine the amount of time before 5% of the drug dose is released from a device when the device is exposed to an appropriate aqueous environment in a United States Pharmacopoeia paddle stirring dissolution apparatus (USP 2) operated at 50 rpm. A lag time of at least 0.5h or longer is considered to be important while a lag time of less than 0.5 h is of little significance. Lag times of more than 4h are desired for delivery of drug into the lower portion of the small intestine while lag times of between 0.5 and 4h are desirable in drug delivery in the upper regions of the gastrointestinal tract.

There are many conditions that demand pulsatile release like [20].

- Many body functions that follow circadian rhythm. E.g. Secretion of hormones, acid secretion in stomach, gastric emptying, and gastrointestinal blood transfusion.
- Chronopharmacotherapy of diseases which shows circadian rhythms in their pathophysiology like bronchial asthma, myocardial infarction, angina pectoris, rheumatic disease, ulcer, and hypertension.
- Drugs that produce biological tolerance demand for a system that will prevent

  their continuous presence at the biophase as this tends to reduce their therapeutic effect.
- The lag time is essential for the drugs that undergo degradation in gastric acidic medium (e.g.: peptide drugs) and irritate the gastric mucosa or induce nausea and vomiting.
- Targeting a drug to distal organs of gastro-intestinal tract (GIT) like the colon requires that the drug release is prevented in the upper two-third portion of the GIT.
- The drugs that undergo first-pass metabolism resulting in reduced bioavailability, altered steady state levels of drug and metabolite, and potential food- drug interactions require delayed release of the drug to the extent possible.

4.1 Advantages and disadvantage of PDDS:

PDDS has unique advantages over other drug delivery systems as it does not release the drug before the desired lag time, resulting in less inter and intra-subject variability, and also avoiding the risk of dose dumping, it releases drug to the right site at the right time and hence improves the bioavailability and stability, reduced adverse effects, and thus improve patient comfort and compliance. Although advantages of PDDS are

many, its only disadvantage is that the rupture time cannot be always adequately manipulated as it is strongly correlated with the physicochemical properties of the polymer [2,4].

4.2 Approaches of PDDS

There are several approaches for the delivery of drugs in a pulsatile manner, mainly using time controlled, stimuli-induced, externally-regulated systems.

a) Time Controlled System

The principle of time controlled drug delivery systems is that the release of the drug happens according to a predetermined rate so to achieve maximum therapeutic and minimum toxic effect. Systems having a lag phase (delayed release systems) and systems where the release is following a biological/circadian rhythm are the most commonly used controlled release systems. As already mentioned the delayed drug release for meeting chronotherapeutical needs provides optimum drug delivery for a number of widespread chronic pathologies. Most delayed release delivery systems are reservoir devices covered with a barrier coating, which dissolves, erodes or ruptures after a lag phase [3,4].

b) Single Unit System

A single unit system mainly includes capsule-shaped and advanced osmotic devices.

1. Capsule Shaped PDDS

The capsule has the capability of delivering therapeutic agents into the body in a time- or position-controlled pulsatile release fashion. A swellable hydrogel plug was used to seal the drug contents into the capsule body. When this capsule comes in contact with the dissolution fluid, it swelled and, after a lag time, the plug pushed itself outside the capsule and rapidly releases the drug. The lag time is controlled by a plug which is pushed away by swelling/erosion and the drug is released as a 'pulse' from the insoluble capsule body. Polymers used for designing this hydrogel plug are various viscosity grades of HPMC, polyvinyl alcohol, PVA, and PEO [3,4].

Bessemer et al[21] have developed and evaluated a pulsatile drug delivery system based on drug-containing hard gelatin capsules coated with a swelling layer and an outer water-insoluble but permeable coating. The lag time rises with expansion of the thickness of the outer coating layer. It can be minimized with the addition of hydrophilic pore former and increment of the thickness of the swelling layer.

Stevens et al[22] used a 5h delay Pulsincap to deliver dofetilide to different sites in the GI tract, employing scintigraphy and pharmacokinetic analysis to evaluate its performance in providing regional drug delivery.

Krogel et al have developed and evaluated a pulsatile drug delivery based on an insoluble capsule body controlled by an erodible plug. Here at first insoluble capsule body was filled with drug and excipients. Plug was prepared either by direct compression or congealing a meltable plug within the capsule opening. The disintegration or erosion time of the plug determines the lag time[23]. Later they have modified the composition of the plug[24]. Here plug composed of pectin and pectinase enzyme. The plug is degraded by the enzyme being present in the plug itself. Sometimes superdisintegrants were used to formulate capsule-based system comprising a drug, swelling agent and rupturable polymer layer[25]. The swelling agent is swelled to rupture completely the polymeric film. This system can be used for delivery of both solid and liquid drug formulations.

Li et al[26] developed a novel system for three pulse drug release based on 'tablets in capsule' device. The objective of their study was to obtain programmed drug delivery from a novel system, which contained a water-soluble cap, impermeable capsule body, and two multilayered tablets, and it was seen that the types of materials for the modulating barrier and its weight can significantly affect the lag time. They selected sodium alginate and HPMC E5 as the modulating barrier material candidate. Through adjusting ratio of sodium alginate/lactose, lag time was controllable between the first two pulsatile releases, and the linear relationship was observed between the ratio and the lag time, whereas lag

time between the second and the third pulse can be successfully modulated by adjusting the ratio of HPMC E5/lactose.

Amidon and Leesma[27] described a drug delivery system for administering a drug in controlled pulse doses to an aqueous environment in the body of a living being. The formulation comprises of one or more, and preferably less than ten, individual drug-containing subunits in a unitary drug depot, such as a tablet or capsule. The individual subunits are designed to dissolve at different sites and/or times in the gastrointestinal tract to release pulse doses of drug into the portal system in an analogous manner to the rate of release from an immediate release dosage form administered according to an appropriate dosing schedule. The dissolution time of the individual subunits can be controlled by several methods including the provision of p^H sensitive enteric coatings and permeability-controlled coatings. The drug delivery system has significant advantages for the oral administration of first-pass metabolized drugs which exhibit a non-linear relationship between input rate of the drug into the portal system and bioavailability.

Jenkins et al[28] described a multiparticulate modified release composition in an erodible, diffusion controlled or osmotic form designed to release the active ingredients at about six to twelve hours so that the resulting plasma profile is substantially similar to the plasma profile produced by the administration of the two or more immediate release dosage forms given sequentially. The composition can be in the form of an erodible formulation in which the structural of the particulates deteriorates within the body over time, in the form of a diffusion controlled formulation in which the particulates are dispersed in a liquid medium or in the form of an osmotic controlled formulation in which the release of the active ingredient from the composition is controlled by osmosis[29].

Percel and coworkers [30] described a capsule capable of delivering therapeutic agents in the body in a time-controlled or position-controlled pulsatile release fashion, composed of one or more populations of multicoated particulates (beads, pellets, granules, etc.). Each bead has been prepared by coating an inert particle such as a non-pareil seed (sugar sphere), with a drug and a polymeric binder or by preparing a drug containing particle by granulation and/or extrusion/ spheronisation, coating the active drug particle with a plasticized enteric coating, and coating plasticized enteric coated drug particle with a mixture of a water insoluble polymer and an enteric polymer. One of the membrane barriers is composed of an enteric polymer while the second membrane barrier is composed of a mixture of water insoluble polymer and an enteric polymer. The composition and the thickness of the polymeric membrane barriers determine the lag time and duration of drug release from each of the bead populations. Optionally, an organic acid containing intermediate membrane may be applied for further modifying the lag time and/or the duration of drug release.

Percel and coworker[31] described a method for manufacturing a multi-particulate dosage form having timed pulsatile release characteristics. The invention provides a novel multicoated particulate dosage form having an active core and a first membrane of an enteric polymer and a second membrane of a mixture of water insoluble and enteric polymers. An organic acid containing membrane between the first and second membrane layers provides time separated pulses. While the membranes can be applied in any order, the enteric polymer membrane is usually applied as the innermost membrane.

Sowden and co-workers[32] described a dosage form for modified release of an active ingredient comprises of two or more cores surrounded by a shell having one or more openings. The openings are distal to one of the cores providing for modified release of one active ingredient upon contact with a liquid medium (the core being distal to the opening). It is possible that the first core contains a pharmaceutically effective dose of a first active ingredient, and the second core contains a pharmaceutically effective dose of a second active ingredient. Each of the first and the second cores could be surrounded by a shell, with a plurality of openings in order to achieve modified release of the second active ingredient upon contact of the dosage form with a liquid

medium. The second core is located distal to all the openings, and all the openings are proximal to only the first core.

2. System Based on Osmosis

Such system consists of capsule coated with the semipermeable membrane. An insoluble plug, osmotically active agent and drug formulations are kept inside the capsule. When capsule shell comes in contact with GI fluid the semipermeable membrane allows the entry of gastric fluid. As a consequence the plug swells and creates osmotic pressure. When this pressure exceeds the tensile strength of the membrane it bursts out and time taken for rupture of the membrane is known as lag time. After lag time the plug is expelled to release the drug [33].

Niwa et al[34] have used capsule made of ethyl cellulose for osmotic based time-specific release of drugs in the colon. The thickness of ethyl cellulose capsule body was varied and the effect of wall thickness on the release of drug was examined. There were numerous micropores at the bottom of the capsule body. Low substituted hydroxyl propyl cellulose was kept in the bottom of the body. Above hydroxyl propyl cellulose mixture of drug, bulking agent and fluorescein were placed. After that the capsule was capped and sealed with a concentrated ethyl cellulose solution. When capsule comes in contact with G.I. fluid water penetrates capsule through micropores and then hydroxyl propyl cellulose swells. As a result internal osmotic pressure is increased causing burst of the capsule shell.

Jimoh et al[35] utilized hollow biodegradable capsules with a thinner membrane at one end to control the lag time of PDDS. In PLA capsule, the effervescent agents like citric acid/sodium bicarbonate were entrapped. As water penetrated into the capsule through the thin PLGA membrane side, an effervescent reaction is generated. Generated carbon dioxide gas accumulates in the capsule which ultimately ruptures the thin membrane. *Jimoh et al* reported that the burst time, i.e. lag time of drug release, can be modulated by varying the dimensions (thickness of the membrane and size) of the capsule and the amount of the effervescent agents**.**

Barzegar-Jalali et al[36] developed an osmotic capsule consisting of hard gelatin capsule filled with acetaminophen, sorbitol as osmotic agent and sodium dodecyl sulfate as release promoter. The capsule shell was coated with semipermeable cellulose acetate containing hydrophobic plasticizer (castor oil) and sealed with white bee's wax. Upon contact with water semipermeable membrane permits the entry of water and osmotic agent dissolves in it. Osmotic pressure is increased inside the shell. It causes the rise of hydrostatic pressure which expels the plug out of the shell and drug is released.

Wong and co-worker[37] described a self-dispersing nano particle active agent formulations developed by dispersing porous particles into which have been sorbed a self-dispersing nano particle active agent formulation in osmotic, push-layer dosage forms providing a continuous or pulsatile delivery of active agents. The dosage form comprises of a wall defining a cavity (the wall having an exit orifice formed or formable and at least a portion of the wall being semipermeable) an expandable layer located within the cavity remote from the exit orifice and in fluid communication with the semipermeable portion of the wall and a drug layer located within the cavity adjacent the exit orifice and in direct or indirect contacting relationship with the expandable layer. The drug layer comprising a self-dispersing nano particle active agent formulation absorbed in porous particles, the porous particles being adapted to resist compaction forces sufficient to form a compacted drug layer without significant exudation of the self-dispersing nano particle active agent formulation.

Linkwitz and coworkers[38] proposed a drug delivery capsule where drug delivery is driven by the osmotic infusion of moisture from a physiological environment. The capsule has a delivery orifice which opens intermittently to achieve a pulsatile delivery effect. The wall in which the orifice is formed is constructed of an elastic material (elastomers) which stretches under a pressure differential caused by the

pressure rise inside the capsule as the osmotic infusion progresses. The orifice is so small that when the elastic wall is relaxed, the flow rate of drug through the orifice is substantially zero, but when the elastic wall is stretched due to the pressure differential across the wall exceeding a threshold, the orifice expands sufficiently to allow the release of the drug at a physiologically beneficial rate.

3. Multiple Unit/Multiparticulate System

The purpose of designing a multi- particulate dosage form is to develop a reliable formulation that has all the advantages of a single unit formulation and yet is devoid of the danger of alteration in drug release profile and formulation behavior due to unit-to-unit variation.

1. System with Erodible, Soluble or Rupturable Membrane

Here a different concept has been utilized. A drug reservoir is coated with a soluble or erodible barrier. Upon dissolution or erosion of that barrier drug is released from the reservoir. These devices are provided with hydrophilic polymeric coatings of adequate thickness. When exposed to aqueous media, these undergo swelling, dissolution and/or erosion phenomena that result in a delayed release of the drug from the core formulation. Lag time is basically programmed by selecting the appropriate polymer and coating level. For this purpose, hydrophilic cellulose derivatives, such as hydroxypropyl methylcellulose (HPMC), hydroxy ethylcellulose (HEC) and hydroxypropylcellulose (HPC), are typically utilized because of their established safety and versatility profiles [39].

Generally eroding systems need thick eroding layers to attain the desired lag times especially when the pellets are small. The problem is that sometimes water soluble drug is released through the swollen barrier. On the other hand, release of drug after lag time is sustained due to remaining barrier materials. In contrast to the swellable or erodible coating systems, system with rupturable membrane depends 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. This system is coated with water-insoluble but permeable membrane. Recently many devices are coated with inner swellable layer and outer rupturable layer. Here release of drug is controlled by the thickness of swellable layer though elasticity and tensile strength of the coating layer may be responsible[39].

Hartman et al[40] developed a multi-particulate PDDS with release properties dependent on the swelling of a UV cross-linked coating and described drug release properties of the developed systems based on a mathematical model. The core consists of MCC and milled sodium chloride coated with a copolymer of methacrylic acid and ethyl acrylate containing trifunctional acrylic monomer pentaerythritol triacrylate as cross-linking agent and a photo-initiator, 2, 2-dimethoxy2 phenylacetophenone. Upon water ingress, the coating swells in such a way that the diffusion coefficient of water increases, making it permeable to the dissolved components in the core. However, the mixed nature of the polymers used in this work resulted in a decrease in the diffusion coefficient initially with an increase in water activity (below 0.4). Thus, *Hartman et al*, from the outcome of this study, reported that the lag time can be controlled by amount of cross-linking, coating thickness, and duration of the UV cross-linking time. The mathematical model developed in this investigation gives good estimation of the lag-time.

Guo et al[41] described Diclofenac sodium pulsatile release pellets by extrusion-spheronisation technology were coated in a mini-fluidized bed spray coater with swelling material as the inner coating swelling layer and ethylcellulose aqueous dispersion as the outer coating controlled layer. The delayed-release time and release rate were influenced by the swelling material, the coating level of the inner swelling layer and the outer controlled layer. Pharmacokinetic and bioavailability studies were performed in eight human subjects. The lag-time for pulsed delivery of Diclofenac was found to be in good agreement between *in-vitro* and *in-vivo*.

Heng et al[42] investigated multilayered pellets, containing neutral core pellets, an inner drug layer, an intermediate HPMC layer (swelling layer) and an outer insoluble diffusion layer, consisting of Eudragit RS. The addition of sodium chloride to the HPMC layer decreased the rate of swelling and thus delayed the bursting of the pellets. This phenomenon was first unexpected because of osmotic effects of the salt, which should promote water uptake. The longer time until rupturing was explained by the competition between sodium chloride and HPMC for the imbibed water**.**

Krogel et al[43,44] have used effervescent mixture of citric acid and sodium bicarbonate in a tablet core coated with ethyl cellulose. The carbon dioxide produced upon contact with water results in rupture of the outer layer leading to drug release. This system is also known as floating pulsatile system. The citric acid can be replaced with tartaric acid. In spite of coating thickness hardness of the core tablet also determines the lag time. This approach can be used in multiple-unit systems. In multiparticulate systems non-pareil sugar seeds are coated with a swellable layer followed by a water-insoluble but permeable layer. The core contains 5 to 60% by weight of the drug based on the total weight of the core. Generally superdisintegrants like sodium carboxymethyl cellulose, sodium starch glycollate, L-hydroxypropyl cellulose, polymers like polyvinyl acetate, polyacrylic acid and polyethylene glycol is used to easily rupture the outer membrane. The lag time can be changed by varying coating thickness or adding high amounts of lipophilic plasticizer in the outermost layer. Rapid release of drug is achieved with high amount of osmotic agent.

Karavas et al[45,46] utilized high-viscosity HPMC/polyvinylpyrrolidone (PVP) composite materials, in which the two polymers were bound by weak interactions rather than simply mixed with each other, were employed as press-coating agents for a Chronopharmaceutical Felodipine delivery system in pursuit of improved reproducibility of performance. Lag time was proven to extend by increasing the HPMC to PVP content ratio. The dissolution rate of Felodipine was enhanced through incorporation into a PVP matrix core as amorphous nanodispersions in order to achieve a fast release after the delay phase.

High-viscosity HPMC grades or combinations of high and low-viscosity ones were used by *Karavas et al*[47,49] for the preparation of a press-coated erodible system containing model drugs with differing solubility properties. When raising the coating level or the high- to low-viscosity polymer ratio, longer lag phases and slower absorption were observed. However, no satisfactory *in vitro-in vivo* correlation could be established. In addition, biphasic slow release patterns with no lag time and double-peak plasma concentration curves were achieved when splitting the drug dose between the core and the coating formulation.

Ishino et al[50] developed pulsatile release tablet. Were rupture of a press-coated layer composed of melted-granulated hydrogenated castor oil and PEG 6000 was induced by the swelling process of calcium carboxymethylcellulose in the core. The delay phase was modulated by changing the thickness and PEG 6000 content of the coating. An *in vivo* evaluation of diltiazem hydrochloride PRT prototypes on beagle dogs pointed out a marked inter-subject variability under fasted conditions and a more reproducible pulsatile release performance in the fed state.

Blum[51] described a controlled release oral dosage form of acetylsalicylic acid (aspirin) capable of delaying the release of the drug until a predetermined time interval after ingestion. The following is prepared in such a manner that, after ingestion, there will be no release for a preset time interval (5-8 hours). Thus, if taken at bedtime it reaches optimal therapeutic blood levels at a time in the early morning when the events leading up to a vascular obstruction culminating in a heart attack or stroke are most commonly occurring after the drug is taken in the evening. The formulation comprises of an aspirin core together with a swelling agent and a frangible coating protecting aspirin from dissolution by gastrointestinal fluids having water soluble and insoluble properties.

Kohn and coworkers[52] uses the degradation products of one polymer to trigger the release of the active compound from another polymer. The delayed release of the active compound was achieved without using a barrier system that requires complex and sophisticated formulation techniques. The proposed formulation comprises the biologically active compound having a chemical structure with hydrogen bonding sites dispersed in a biocompatible, hydrolytically degrading polyarylate. In the case of peptide drugs, interactions between the peptide and the first polymer inhibit the release of the peptide. Bonding interactions between the polymer and the active compound are used to lock the active compound into the polymeric matrix. The second polymer can be degraded into acidic byproducts into the matrix. This is necessary because the hydrogen bonding interactions can be weakened under conditions of low p^H, resulting in the release of the peptide. Degradation products lower the p^H of the matrix, causing an interruption in the interactions and the subsequent release of the peptide.

Sturak et al[53] described an invention that provides a controlled release solid dosage form of flutamide. The system is designed to provide an immediate release dose and a second delayed dose in the gastrointestinal tract for twice a day use. The desired release is obtained by forming a core containing a rapidly dissolving solid dispersion of flutamide in a carrier which is capable of forming a solid dispersion with flutamide. The release of flutamide from the core is delayed by coating the core tablet with a barrier or enteric coating. A layer of flutamide is then applied to the coated core tablet to provide the immediate release initial dose. The core of the novel tablet formulation provides the second dose of this invention comprising 20 to 80 percent by weight of the total amount of flutamide in the tablet and a carrier capable of forming a solid dispersion with flutamide.

2. Systems with Change Membrane Permeability

Sigmoidal release pattern is therapeutically beneficial for timed release and colon-specific drug delivery and is observed in coated systems. Sigmoidal release pattern is therapeutically beneficial for timed release and colonic drug delivery, and is observed in coated systems. A sigmoidal release pattern is reported based on the permeability and water uptake of Eudragit RS or RL, influenced by the presence of different counter-ions in the release medium[1,2].

Based on this concept, *Narisawa et al*[54,55] developed a device capable of giving pulse release depending on the change in diffusion properties of Eudragit RS. They found that a theophylline core coated with Eudragit RS showed very slow release rates in pure water which increases significantly when the microcapsules were immersed in an organic acid solution containing succinic, acetic, glutaric, tartaric, malic, or citric acid. They opined that this could be because of higher hydration of the film containing quaternary ammonium groups on interaction with the acids. The drug release rate from the beads coated with Eudragit NE 30D, which has no quaternary ammonium groups in the polymer chain, was not affected by succinic acid, suggesting that the quaternary ammonium groups of Eudragit RS are essential to produce the unique drug release profile. When succinic acid was incorporated into the core of Eudragit RS-coated theophylline beads, the drug release profile showed a typical sigmoidal pattern.

In another similar system, theophylline and sodium acetate, acting as the permeability modifying salt, were layered on sugar pellets, followed by coating with Eudragit RS. The lag time increased with increasing thickness of the outer membrane. However, the slope of the drug release phase was independent of the thickness but was influenced by the amount of the salt in the system, indicated that the release mechanism is depend on the amount of the salt or permeability modifier [56].

Stevens et al[57] have used extrusion/spheronisation technology to produce a novel pellet formulation containing diltiazem that was coated with a mixed film coat comprising ethylcellulose and Eudragit RS polymers. While the ethylcellulose component acted as a diffusion barrier retarding release of diltiazem, the

permeability of the Eudragit RS increased progressively. The overall effect was a sigmoidal release profile.

Gendrot and coworkers[58] described a formulation of a multiparticulate pharmaceutical form of a delayed and/or pulsed release, enabling to obtain the onset of the availability of the active ingredient within 4 to 8 hours after the ingestion of the pharmaceutical form, and then a progressive release of the totality of the active ingredient within the 8 to 20 following hours. The formulations is in the form of spheroids consisting of a neutral spherical core comprising a first coating based on a mixture of at least one hydrosoluble polymer and of at least one non hydrosoluble polymer throughout which the constitutive particles of an active ingredient are uniformly distributed. A second coating based on at least two p^H independent polymers presenting rates of permeability different from one another with respect to the gastric and intestinal mediums, was also used.

Chen[59] described a system composed of a large number of pellets made up of two or more populations of pellets or particles. Each pellet contains a drug containing core, and a water soluble osmotic agent enclosed in a water permeable, water-insoluble polymer film. Incorporated into the polymer film is a hydrophobic, water insoluble agent which alters the permeability of the polymer film. The film coating of each population of pellets differs from the coating of every other population of pellets in the dosage form in the rate at which water passes through to the core and the rate at which drug diffuses out of the core. The osmotic agent dissolves in the water, causing the pellet to swell and regulating the rate of diffusion of drug into the environment of use. As each population of pellets releases drug into the environment sequentially, a series of pulsatile administrations of the drug from a single dosage form is achieved.

3. Low Density Floating Multi-Particulate Pulsatile Systems

Conventional Multiparticulate pulsatile release dosage forms mentioned above are having longer residence time in the gastrointestinal tract and due to highly variable nature of gastric emptying process may result in-vivo variability and bioavailability problems. In contrary, low density floating Multiparticulate pulsatile dosage forms reside in stomach only and not affected by variability of p^H, local environment or gastric emptying rate. These dosage forms are also specifically advantageous for drugs either absorbed from the stomach or requiring local delivery in stomach. Overall, these considerations led to the development of Multiparticulate pulsatile release dosage forms possessing gastric retention capabilities[4].

Sharma et al[60] developed a multiparticulate floating-pulsatile drug delivery system was developed using porous calcium silicate (Florite RE) and sodium alginate, for time and site specific drug release of Meloxicam for Chronopharmacotherapy of rheumatoid arthritis. Meloxicam was adsorbed on the Florite RE (FLR) by fast evaporation of solvent from drug solution containing dispersed FLR. Drug adsorbed FLR powder was used to prepare calcium alginate beads by ionotropic gelation method, using [32] factorial designs. The floating time for this system was controlled by density of beads and hydrophobic character of drug.

Sher et al[61] combined floating and pulsatile principles were achieved using a specific technology, in which low density microporous polypropylene, Accurel MP 1000, were used as a multiparticulate carrier for ibuprofen. Ibuprofen was adsorbed on the polymer by solvent evaporation technique; a single step method resulted in to different porous particles. This drug delivery system showed distinct behaviour from other approaches in chronotherapy with desired low drug release in acidic medium, reduced time consumption due to single step process, and even overcame the limitations of process variables caused by multiple formulation steps.

Badve et al[62] developed hollow calcium pectinate beads for floating-pulsatile release of Diclofenac sodium intended for Chronopharmacotherapy of rheumatoid arthritis. To overcome limitations of various approaches for imparting buoyancy, hollow/porous calcium

pectinate beads were prepared by a simple process of acid-base reaction during ionotropic cross-linking. The floating beads provided two phase release patterns with an initial lag time during floating in acidic medium followed by rapid pulse release in phosphate buffer. This approach suggested the use of hollow calcium pectinate microparticles as promising floating PDDS for site- and time-specific release of drugs.

b). Stimuli Induced Systems

Several polymeric delivery systems undergo phase transitions and demonstrate marked swelling-de-swelling changes in response to environmental changes including solvent composition, ionic strength, and temperature .Responsive drug release from those systems results from the stimuli-induced changes in the gels or in the micelles, which may de-swell, swell, or erode in response to the respective stimuli [3,4].

a) Temperature-Induced System:

Use of temperature as a stimulus has been justified by the fact that the body temperature often deviates from the physiological temperature in the presence of pathogens or pyrogens. This deviation sometimes can be a useful stimulus to activate the release of therapeutic agents from various temperature-responsive drug delivery systems [63].

1. Thermoresponsive Hydrogel System

Okano et al [64, 65] developed the PIPAAm crossed linked Thermoresponsive gel. PIPAAm cross-linked gels have shown thermoresponsive, discontinuous swelling/de-swelling phases, i.e. swelling at temperatures below 32°C, while shrinking above this temperature. A sudden temperature increase above the transition temperature of these gels results in the formation of a dense, shrunken layer on the gel surface 'skin layer', which hinders the water permeation from inside the gel into the environment. Drug release from the PIPAAm hydrogels at temperatures below 32°C was governed by diffusion, while above this temperature drug release stops completely due to the 'skin layer' formation on the gel surface (on-off drug release regulation).

Another rapid deswelling phase was achieved by incorporating poly (ethylene glycol) graft chains in PIPAAm cross linked hydrogels. Hydrogen bonded polymeric gel has been used as thermo-responsive drug delivery system. The mixture of poly (ethylene oxide)-poly (propylene oxide) poly (ethylene oxide) triblock copolymer and polyvinyl alcohol forms a complex polymeric gel by intra or inter molecular hydrogen bonding. Based on the temperature-sensitivity of hydrogen bondings in this complex gel, thermo-responsive pulsatile drug delivery system has been designed and characterized. For the stability in the aqueous media, the gel was prepared with a form of polymeric bead, followed by the encapsulation with poly (lactide-co-glycolide) membrane. The swelling transition of polymer complex gel was manipulated by changing the ratio of these polymers. Using acetaminophen as a model drug pulsatile release was revealed in between 35 °C and 40 °C [66].

Kaneko et al[67,69] developed rapid de-swelling phase by incorporating PEG graft chains into PIPAAm cross linked hydrogels. The introduction of PEG chains did not alter the transition temperature as it was seen in the gels with hydrophilic co-monomers, such as acrylamide and acrylic acid, which may be due to the structural independence of the PEG chains from the cross-linked PIPAAm main chains. In this case, however, the de-swelling mechanism is different from PIPAAm graft-type hydrogels. During the shrinking process, the graft PEG chains form hydrophilic channels for water molecules, most likely due to a phase separation within the shrinking gels leading to a rapid de-swelling. The majority of the drugs in the gels were released through the PEG formed channels with water molecules. As mentioned above, accelerated de-swelling of cross-linked hydrogels is achieved by the introduction of graft chains independent from gel main chains. As these gels can be activated by external stimuli they are utilized for drug release at targeted areas.

2. Thermoresponsive Polymeric Micelle System

Thermo-responsive polymeric micelle systems are fruitful for targeted drug delivery because of their unique features like reliable structural stability, nano-order diameter and hydrophobic drug solubilization in aqueous medium. These micelles are not detected by body defense mechanism i.e. reticuloendothelial system and accumulate loaded drugs preferentially in solid tumor tissues through the enhanced permeability and retention [4].

Akimoto et al[70] used thermo-responsive micelle drug carrier systems composed of conventional site-specific drug targeting with temporal drug targeting modulated by local cancer therapeutic heating, hyperthermia. They prepared surface-functionalized polymeric micelles with well-defined end-functionalized amphiphilic diblock copolymers using reversible addition fragmentation chain transfer radical polymerization.

b). Chemical Stimuli Induced System

A biochemical change in the physiology of human beings is utilized as a stimulus for triggering drug release from the pulsatile system.

1. 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, p^H or any other chemical stimuli. 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 and in very severe cases the condition may lead to death. The injection of insulin at the proper time is thus necessary for the treatment of diabetic patients. Self-injection is painful and has sometimes led to the development of a hypoglycemic coma, due to an overdose of insulin. In other cases, an insufficient amount of injected insulin has led to hyperglycemia and an insufficient therapeutic effect. Thus, a great demand has arisen for the precise, effective delivery of insulin to insure normal blood glucose levels. For these purpose a novel approach for the release of insulin, development of stimuli-responsive hydrogels which respond to glucose concentration changes were carried out by various scientist[4].

Obaidat et al[71,72] developed a copolymer of acrylamide and allyl glucose. The side-chain glucose units in the copolymer were bound to Con A. These hydrogels showed a glucose-responsive, sol-gel phase transition based on the external glucose concentration. The non-linear dependence of this sol-gel phase transition with regard to the glucose concentration was not only due to the increased binding affinity of allyl glucose to Con A compared to native glucose, but also due to the cooperative interaction between glucose containing copolymer and Con A.

Kataoka et al[73] developed glucose and Thermoresponsive hydrogels using acrylamidophenylboronic acid and PIPAAm. The obtained gels, containing 10 mol% phenylboronic acid moieties, showed a transition temperature of 22°C in the absence of glucose. Below this temperature the gels existed in a swollen state. The introduction of glucose to the medium altered the transition temperature of the gels in such a way that the transition temperature increases with increasing glucose concentration to reach 36°C at 5.0 g/l glucose concentration. Boronic acid was in equilibrium between the undissociated (uncharged) and the dissociated (anionically charged) form. With increasing glucose concentration, the equilibrium shifted to increase the amount of dissociated boronate groups and the gels become more hydrophilic**.**

2. Inflammation Induced System

On receiving any physical or chemical stress, such as injury, fracture etc., inflammation take place at the injured sites. During inflammation, hydroxyl radicals are produced from these inflammation-responsive cells. 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 poly-morphonuclear cells play a role in the healing process of the injury. During inflammation, hydroxyl radicals (OH) are produced from these inflammation-responsive cells. They focused on these inflammatory-induced hydroxyl radicals and designed drug delivery systems, which responded to the hydroxyl radicals and degraded in a limited manner[74, 75].

3. Drug Release from 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 the concentration of bioactive compounds to alter their swelling/de-swelling characteristics.

Miyata et al[76,77] focused on the introduction of stimuli-responsive cross-linking structures into hydrogels. Special attention was given to antigen-antibody complex formation as the cross-linking units in the gel as specific antigen recognition of an antibody can provide the basis for a new device fabrication. Utilizing the difference in association constants between polymerized antibodies and naturally derived antibodies towards specific antigens, reversible gel swelling/de-swelling and drug permeation changes can be obtained. This study proved that the biological stimuli-responsive hydrogels can be successfully created.

4. P^H Sensitive Drug Delivery System

The P^H differential between the stomach and small intestine has historically been exploited in oral drug delivery. Significant variations in the P^H occur in the GI tract with values ranging from approximately 1.2 in the stomach, to 6.6 in the proximal small intestine and a peak of about 7.5 in the distal small intestine followed by a sharp decline in colon where the luminal p^H is below 7[78]. A particular p^H is used as a triggering point of drug release from such delivery system. That device can be made of using p^H dependent polymer in such a manner that the drug will be released after reaching particular surrounding p^H of the device. P^H sensitive polymers are polyelectrolytes that bear in their structure weak acidic or basic groups that either accept or release protons in response to changes in environmental p^H. In case of p^H dependent system advantage has been taken of the fact that there exists different p^H environment at different parts of the GIT. By selecting the p^H dependent polymers drug release at specific location can be obtained. Examples of p^H dependent polymers include cellulose acetate phthalate, polyacrylates, and sodium carboxy methyl cellulose. These polymers are used as enteric coating materials so as to provide release of drug in the small intestine.

Several coated systems that utilize the p^H differential in the GI tract have been used to target various delivery sites in the intestinal lumen. A patent on a p^H controlled pulsatile delivery system has been recently published, describing a formulation were a core is surrounded by a p^H sensitive coating material in which a swellable agent is embedded underneath an enteric coat. The enteric coating material erodes upon a change in p^H and then GI fluid reaches the swellable agent which swells enough to accelerate the disintegration of the coating and to cause instant release of the drug at the target site[79]. P^H Controlled drug release at a specific target site can be achieved by the use of a single polymer or a combination of polymers. Such coating polymers can be selected from the group consisting of cellulose, hydroxypropyl methylcellulose, and various Eudragits. The coating layer may contain also a plasticizer. In another example drug delivery composition consisting of a complex between polyvinylpyrrolidone and other synthetic polymers like poly (maleic diacid-alkyl vinyl ether) have been proved to target the proximal part of small intestine [80], while dosage forms coated with the acrylic polymer Eudragit S, an excipient known to have a threshold p^H for dissolution, has been successfully target distal gut. *Schellekens et al*[81] developed new systems for site-specific pulsatile delivery in the ileo-colonic regions are described. The capsules were manually filled with a premix of active ingredient and excipients (Avicel PH100 and colloidal anhydrous silica). The capsules were coat with

different coating suspensions. Which containing polyethylene glycol and Eudragit S was added slowly to allow it to dissolve. To this mixture a disintegrant may be added. The coating suspension was applied to capsule. The system is based on the non-percolating incorporation of disintegrant in a coating which consists further of a continuous matrix of p^H responsive polymer (Eudragit S). A proof of concept study in human subjects was performed to investigate the performance of the new system *in-vivo*. Coated capsules containing the stable isotope glucose as the test compound were administered and the occurrence of [13] CO_2 in the breath of the subjects was measured. It could be shown that the coating is able to resist the environmental conditions in the stomach and duodenum and delay release until deeper parts of the intestines are reached. Furthermore, the capsule is able to maintain a pulsatile release profile.

Kadam et al[82] formulated and evaluated fast release enteric-coated tablets for pulsatile drug release to the colon. The novelty of this work was the combination of p^H and time dependent enteric polymers as a single coating agent. Eudragit S100 was used as a p^H dependent polymer, Eudragit RL100 was used as a time dependent polymer, and theophylline was chosen as a model drug. Dissolution studies of enteric-coated tablets were performed with different media having a p^H of 1.2, 6.8, and 7.4. Results of the dissolution data showed that drug release in the colon could be controlled by using Eudragit RL100 and Eudragit S100. The lag time prior to the drug release was highly affected by a combination of two factors, namely the percentage of Eudragit RL100 and coating level. The optimum formulation was found to be one containing Eudragit RL100 and Eudragit S100, with a ratio of 60:40 of polymer and coating level of 4.66% w/w. The present study demonstrated that the theophylline enteric-coated tablets could be successfully formulated as a PDDS by the design of a time and p^H dependent modified Chronopharmaceutical formulation.

Dedhiya and co-workers[83] described a modified release composition of lercanidipine, based on the p^H of the use environment. The formulation provides a multiple pulses p^H dependent release bead composition, incorporating an immediate release bead containing lercanidipine and a first layer comprising at least one p^H dependent release modifying polymer. The formulation consists from an inert core, a first layer comprising a permeability and solubility enhancing surfactant, a binder and lercanidipine, and optionally, a second layer comprising a film coating. The first pulse (immediate release) releases 80% of the drug in the layer within 60 minutes following exposure to p^H from 1.2 to 4.5, (simulating fasting and fed stomach p^H). The second pulse releases 80% of the drug in the core within 180 minutes following exposure to p^H greater than about 5.6. Alternatively, the second pulse has a p^H dependent compositiona1 unit dosage of the active that is released following exposure to p^H greater than about 6.2 and 6.8 simulating the p^H of small intestine and the ileum region respectively. This layer comprises of at least one p^H dependent release modifying polymer; and optionally, a second layer comprising a film coating (Eudragit-L, Eudragit-S®, Acryl-Eze® and combinations thereof).

Sharma[84] described a delayed release drug delivery system containing an acid sensitive drug which is stable at p^H levels above 9.0, such as omeprazole. The delayed release drug delivery system is comprised of an alkaline core structure, layered omeprazole dispersion (aqueous dispersion of a water soluble binder), a separation barrier, (a non-enteric moisture barrier) and a delayed release enteric barrier providing gastro-resistant behavior to deliver omeprazole in the proximal segment (p^H 5-6) of the gastrointestinal tract. The goal is to take advantage of the alkaline core structure for optimization of release and stability of acid sensitive drugs and so to provide a delayed release dosage form of an acid sensitive drug, such as omeprazole which is resistant to dissolution in acidic media. Another aspect is to provide a sub-separation layer in the pellets adjacent to a layer containing the active acid sensitive material, the subseparation layer comprising water soluble/water dispersible polymer and a pharmaceutically acceptable water soluble buffer which can provide a p^H of at least 9.0. The use of the high buffer materials assures

that even in the presence of moisture which could cause migration of acid within the pellets, the high p^H buffer would reduce any effect that migratory acid could have on the system.

c) Externally Regulated System

For releasing the drug in a pulsatile manner, another way can be the externally regulated systems in which drug release is programmed by external stimuli like magnetism, ultrasound, electrical effect and irradiation. In this drug delivery are not self-operated, but instead required externally generated environmental changes to initiate drug delivery.

1. Magnetically stimulated system

Magnetic carriers receive their magnetic 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. Use of an oscillating magnetic field to modulate the rates of drug delivery from a polymer matrix was one of the first methodologies investigated to achieve an externally controlled drug delivery system **[85].**

Brazel et al[86] has development of magneto thermally-triggered drug delivery systems, where by magnet i.e. nanoparticles are combined with thermally-activated materials. By combining super paramagnetic nanoparticles with lower critical solution temperature (LCST) polymers, an alternating current (AC) magnetic field can be used to trigger localized heating *in-vivo*, which in turn causes a phase change in the host polymer to allow diffusion and release of drugs**.**

Saslawski et al[87] developed different formulations for in vitro magnetically triggered delivery of insulin based on alginate spheres. In an experiment, ferrite microparticles (1µm) and insulin powder were dispersed in sodium alginate aqueous solution. The ferrite-insulin alginate suspension was later dropped in aqueous calcium chloride solution which causes the formation of cross linked alginate spheres, which were further cross linked with aqueous solution of poly(L-lysine) or poly(ethylene imine). They described that the magnetic held characteristics due to the ferrite microparticles and the mechanical properties of the polymer matrices could play role in controlling the release rates of insulin from the system.

Handy et al[88] provides a treatment method that involves the administration of a magnetic material composition, which contains single-domain magnetic particles attached to a target-specific ligand, to a patient and the application of an alternating magnetic field to inductively heat the magnetic material composition, which cause the triggered release of therapeutic agents at the target tumor or cancer cells.

Tingyu Liu et al[89] developed the magnetic hydrogels by chemically cross linking of gelatin hydrogels and Fe_3O_4 nanoparticles (ca. 40–60 nm) through genipin (GP) as cross-linking agent. Moreover, *in-vitro* release reveals that drug release profile of the resulting hydrogels is controllable by switching on or off mode of a given magnetic field. Based on this on-and-off mechanism, the smart magnetic hydrogels based on the gelatin-ferrite hybrid composites can be potentially developed for application in novel drug delivery systems.

Babincova et al[90] developed magneto-liposomes for triggered release of drug. In their delivery systems, they entrapped dextran-magnetite and model drug, 6-carboxyfluorscein in the liposomes and used a laser to trigger the release of the drug. The magnetite absorbs the laser light energy to heat the lipid bilayer above the gel-liquid crystal phase transition temperature Tc, which is 41°C for dipalmitoylphosphatidylcholine. Liposomes made from this lipid release their content as soon as temperature is reached to this level. They also suggested that the absorption of laser energy by magnetite particles provide a means for much localized heating and controlled release of liposome with a single laser pulse. This may have potential applications for selective drug delivery, especially to the eye and skin. Even though the magnetic modulated therapeutic approach is one of the promising approaches for PDDS, it still needs very careful attention for a number of physical and magnetism-related properties. The magnetic force, which is defined by its field and field gradient needs to be large and carefully

shaped to activate the delivery system within the target area and the magnetic materials, should be tissue stable and compatible.

Saslawski et al[91] has developed different formulations for *in-vitro* magnetically triggered delivery of insulin based on alginate spheres. In an experiment, ferrite microparticles (1 mm) and insulin powder were dispersed in sodium alginate aqueous solution. The ferrite-insulin-alginate suspension was later dropped in aqueous calcium chloride solution which causes the formation of cross linked alginate spheres, which were further cross linked with aqueous solution of poly (lysine) or poly (ethylene imine). Applications as high frequency gave a significant release enhancement for the second magnetic field application, after which the enhancement level decreased due to the faster depletion at these frequencies.

2. Ultrasonically Stimulated System

Ultrasound is mostly used as an enhancer for the improvement of drug permeation through biological barriers, such as skin, lungs, intestinal wall and blood vessels. There are several reports describing the effect of ultrasound on controlled drug delivery. The interactions of ultrasound with biological tissues are divided into two broad categories: thermal and nonthermal effects. Thermal effects are associated with the absorption of acoustic energy by the fluids or tissues[92]**.** Non-thermal bio-effects are generally associated with oscillating or cavitating bubbles, but also include non-cavitations effects such as radiation pressure, radiation torque, and acoustic streaming. With respect to drug delivery, these latter effects are probably not involved except to the degree that fluid or particle motion (via acoustic streaming or radiation pressure) increases convection and transport of drug. Bio-effects related to cavitations can produce strong stresses on cells, which may increase drug interactions with the cell, including increased transport toward and into the cell.

Hussain et al[93] the high toxicity of potent chemotherapeutic drugs like doxorubicin (Dox) limits the therapeutic window in which they can be applied. This window can be expanded by controlling the drug delivery in both space and time such that nontargeted tissues are not adversely affected. Recent research has shown that ultrasound (US) can be used to control the release of Dox and other hydrophobic drugs from polymeric micelles in both time and space. Dox activity can be enhanced by ultrasound in one region, while in an adjacent region there is little or no effect of the drug. They review the *in-vivo* and *in-vitro* research being conducted in the area of micellar drug delivery and ultrasound to cancerous tissues. Attempt to represent the release and reencapsulation phenomena of DOX from pluronic P105 micelles upon the application of ultrasound.

Kost et al[94] described an ultrasound-enhanced polymer degradation system. During polymer degradation incorporated drug molecules were released by repeated ultrasonic exposure. As degradation of biodegradable matrix was enhanced by ultrasonic exposure, the rate of drug release also increased. Thus, pulsed drug delivery was achieved by the on-off application of ultrasound.

Calcium alginate can be utilized as polymer for ultrasound moderated drug delivery. *Lanting and Barrett*[95] used this polymer for encapsulation of calcium carbonate suspension which is sensitive to ultrasound. This factor is helpful for determining the lag time because increasing concentration of calcium carbonate leads to lowering of disintegration time of spheres.

A macromolecular drug dextran has shown burst release from porous poly (L-lactic) acid microspheres under low ultrasonic energy [96]. At moderate loading level whole drug was released during burst phase. But at lower loading level release was reduced i.e. whole drug was released at a time. Remaining portion after burst release came to the medium continuously for long time.

3. Electrically Stimulated System

Polyelectrolytes (polymers which contain relatively high concentration of ionisable groups along the backbone chain) and are thus, p^H-responsive as well as electro-responsive. An electric field as an external stimulus for triggering the drug release is advantageous due to the

availability of equipment which allows precise control with regards to the magnitude of current, duration of electric pulses, interval between pulses, etc. Under the influence of electric field, electro-responsive hydrogels generally deswell or bend, depending on the shape of the gel lies parallel to the electrodes whereas deswelling occurs when the hydrogel lies perpendicular to the electrodes.

Synthetic as well as naturally occurring polymers separately or in combination have been used. Examples of naturally occurring polymers include hyaluronic acid, chondroitin sulfate, agarose, carbomer, xanthan gum, and calcium alginate. The synthetic polymers are generally acrylate and methacrylate derivatives such as partially hydrolyzed polyacrylamide, polydimethylaminopropyl acrylamide[97, 98].

Kulkarni et al[99] developed electroresponsive drug delivery system using poly (acrylamide-grafted-xanthan gum) (PAAm-gXG) hydrogel for transdermal delivery of ketoprofen. The electrically sensitive PAAm-g-XG copolymer was synthesized by free radical polymerization under nitrogen atmosphere followed by alkaline hydrolysis. The electroresponsive drug delivery system (EDDS) was prepared by entrapping the hydrogel within a shallow compartment molded from a backing layer and rate controlling membranes (RCM). When a swollen PAAm-g-XG hydrogel was placed in between a pair of electrodes, deswelling of the hydrogel was observed in the vicinity of electrodes carrying the electric stimulus. The membrane-controlled drug delivery systems were prepared using drug-loaded PAAm-g-XG hydrogel as the reservoir and crosslinked with poly (vinyl alcohol) to form films as rate controlling membranes (RCM). A pulsated pattern of drug release was observed as the electric stimulus was switched 'on' and 'off.' These PAAm-g-XG hydrogel could be useful as transdermal drug delivery systems actuated by an electric signal to provide on-demand release of drugs.

Grayson et al[100] used of microfabrication techniques to produce microelectro mechanical systems (MEMS) has allowed engineers to address a wider range of clinical indications. A new direction in the area of MEMS technology is the goal of achieving pulsatile drug delivery. The digital capabilities of MEMS may allow greater temporal control over drug release compared to traditional polymer-based systems. A repertoire of structures, including microreservoirs, micropumps, valves, and sensors, is being developed that will provide a strong foundation for the design of integrated, responsive MEMS for drug delivery.

Murdan et al[101] were developing electrically controllable drug release from polyelectrolyte hydrogels has been demonstrated *in-vitro* and *in-vivo*. Pulsatile drug release profiles, in response to alternating application and removal of the electric field have been achieved. Responsive drug release from hydrogels results from the electro-induced changes in the gels, which may deswell, swell or erode in response to an electric field. The mechanisms of drug release include ejection of the drug from the gel as the fluid phase synereses out, drug diffusion along a concentration gradient, electrophoresis of charged drugs towards an oppositely charged electrode and liberation of the entrapped drug as the gel complex erodes.

Yuk, et al[102] developed monolithic devices which composed of sodium alginate and polyacrylic acid was prepared. A pulsatile drug release pattern was observed upon application of electrical current using the prepared monolithic devices. Two release patterns of hydrocortisone were achieved by proper design of the drug delivery devices, demonstrated the feasibility of achieving a pulsatile drug delivery system depending on the environmental condition.

4. Photo-Stimulated System

The interaction between light and material can be used to modulate drug delivery. This can be accomplished by combining a material that absorbs light at a desired wavelength and a material that uses energy from the absorbed light to modulate drug delivery. Embedding the nanoshells in a NIPAAm-co-AAM hydrogel formed the required composite material. When exposed to near infrared light, nanoshells absorb the light and convert it to heat, raising the

temperature of composite hydrogel above its LCST. That's result in the increase rate release of the drug from matrix system [103].

Light-sensitive hydrogels have potential applications in developing optical switches, display units, and ophthalmic drug delivery devices. Since the light stimulus can be imposed instantly and delivered in specific amounts with high accuracy, light-sensitive hydrogels may possess special advantages over others [104]. For example, the sensitivity of temperature, sensitive hydrogels is rate limited by thermal diffusion, while p^H-sensitive hydrogels can be limited by hydrogen ion diffusion. The capacity for instantaneous delivery of the sol-gel stimulus makes the development of light sensitive hydrogels important for various applications in both engineering and biochemical fields. Light sensitive hydrogels can be separated into UV-sensitive and visible light-sensitive hydrogels. Unlike UV light, visible light is readily available, inexpensive, safe, clean and easily manipulated.

5. Mechanical Force:

Mechanical force can also be used for the development of drug delivery system with pulsatile effect. Alginate hydrogels containing vascular endothelial growth factor have been developed[105]. Mechanical compression is applied to liberate drug held within the polymeric hydrogels. The release rate and cumulative release of the drug enhance during compression. Like elastic material this hydrogel comes to the original phase upon relaxation of compression force. But at the end of each relaxation cumulative release is similar to controlled or non-compressed hydrogels. In this condition drug does not bind to hydrogels and mechanical force can't guide significantly, the release behavior of drug due to rapid depletion of the incorporated drug from the hydrogels.

6. Conclusion:

With the increase in the awareness of the dosage regimen and hectic life style, experts forecast a continuously rising demand for dosage forms with pulsatile drug release. Thus, more and more attempts are being made to adjust drug delivery systems accurately to patient requirements, both in terms of therapeutic efficacy and compliance. In the present review, we have described various system developed by researchers working in the development of PDDS.

7. References

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