



A REVIEW ON PULSATILE DRUG DELIVERY SYSTEM

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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 and temporal delivery and increasing patient compliance. Pulsatile Drug Delivery systems (PDDS) are basically time-controlled drug delivery systems in which the system controls the lag time independent of environmental factors like pH, enzymes, gastro-intestinal motility, etc. These systems are designed according to the circadian rhythm of the body. 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 where night time dosing is required, such as anti-arrhythmic and anti-asthmatic. Some of the disease conditions wherein PDDS are promising include duodenal ulcer, cardiovascular diseases, arthritis, asthma, diabetes, neurological disorder, cancer, hypertension and hypercholesterolemia. PDDS can be classified into time controlled systems wherein the drug release is controlled primarily by the delivery system, stimuli induced PDDS in which release is controlled by the stimuli, such as the pH or enzymes present in the intestinal tract or enzymes present in the drug delivery system and externally regulated system where release is programmed by external stimuli like magnetism, ultrasound, electrical effect and irradiation. 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, limitation, and Polymers used in pulsatile drug delivery system. To introduce the concept of chronotherapeutics, it is important to define the following concepts.

Key words: Pulsatile Drug Delivery Systems, chronotherapeutic, controlled systems, polymers.

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 process¹. Traditionally, drug delivery has meant for getting a simple chemical absorbed predictably from the gut or from the site of injection. The oral controlled release system shows a typical pattern of drug release figure 1 in which the drug concentration is maintained in the therapeutic window for a prolonged period of time (sustained release), thereby ensuring sustained therapeutic action.

A second-generation drug delivery goal has been the perfection of continuous, constant rate delivery of bioactive agents. However, living organisms are not “zero-order” in their requirement or response to drugs. They are predictable resonating dynamic circadian cycle which will maximize desired and minimize undesired drug effects² Figure 2. Till early nineties efforts have been made to design the drug delivery system which will release the drug at fairly constant rate. In fact these systems turned to be one of the most successful systems in delivering the drug molecule³. But still for many of the drugs, use of such systems is not suitable because of a number of reasons. This is particularly true in cases where the drug is subjected to large metabolic degradation. Due to ‘first pass effect’ there will be reduction in the bioavailability of the drug because; gradual release can result in greater degradation. Secondly drugs with short half-life need to be administered repeatedly which results in patient non-compliance. Further, in case of chronic treatment, where the drug is given in sustained release dosage form,

continuous exposure of the drug to body may lead to adverse effect. For example, diabetes mellitus requires chronic treatment with sustained release formulations of drugs like sulfonylurea which will damage the pancreas earlier than the corresponding immediate release dosage form. Lastly, drugs which exhibit tolerance should not be delivered at a constant rate, since the drug effect decreases with time at constant drug level. In addition drug toxicity increases with time when drug levels are held constant. In such cases it is preferable to opt for dosage form which will provide desired concentration of drug at particular time point only⁴. Nowadays, concept of chronopharmaceutics has emerged, wherein, research is devoted to the design and evaluation of drug delivery systems that release a therapeutic agent at a rhythm that ideally matches the biological requirement of a given disease therapy. Diseases where a constant drug levels are not preferred, but needs a pulse of therapeutic concentration in a periodic manner acts as a push for the development of “Pulsatile Drug Delivery Systems”⁵. In these systems, there is rapid and transient release of a certain amount of drug molecules within a short time-period immediately after a predetermined off release period Figure 3. Various techniques are available for the pulsatile delivery like pH dependent systems, time dependent systems, micro-flora activated systems, etc. which can be designed as per the physiology of disease and properties of the drug molecule. The focus of the present review is primarily on the pulsatile drug delivery methodologies and the upcoming technologies, which are being exploited on an industrial scale.

Advantages and Drawbacks of Pulsatile drug delivery systems

Advantages

- Predictable, reproducible and short gastric residence time
- Less inter- and intra-subject variability

- Improve bioavailability
- Reduced adverse effects and improved tolerability
- Limited risk of local irritation
- No risk of dose dumping
- Flexibility in design
- Improve stability
- Improve patient comfort and compliance
- Achieve a unique release pattern
- Extend patent protection, globalize product, and overcome competition

Drawbacks

- Lack of manufacturing reproducibility and efficacy
- Large number of process variables
- Multiple formulation steps
- Higher cost of production
- Need of advanced technology
- Trained/skilled personal needed for manufacturing

Chronobiology⁶

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

Chronopharmacology

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

Chronopharmacokinetics⁷

Chronopharmacokinetics involves study of temporal changes

in drug absorption, distribution, metabolism and excretion. Pharmacokinetic parameters, which are conventionally considered to be constant in time, are influenced by different physiological functions displaying circadian rhythm. Circadian changes in gastric acid secretion, gastrointestinal motility, gastrointestinal blood flow, drug protein binding, liver enzyme activity, renal blood flow and urinary pH can play role in time dependent variation of drug plasma concentrations.

Chronotherapy

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

Chronotherapeutics⁸

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

Biological rhythms⁹

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

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

Circadian rhythms: Circadian rhythms are self-sustaining, endogenous oscillations.

Table 1: Diseases requiring Pulsatile Drug Delivery

Disease	Chronological behaviour	Drugs used
Peptic ulcer	Acid secretion is high in the afternoon and at night	H ₂ blockers
Asthma	Precipitation of attacks during night or at early morning hour	β ₂ agonist, Anticholinergic
Cardiovascular diseases	BP is at its lowest during the sleep cycle and rises steeply during the early morning awakening period	Nitroglycerin, Calcium channel blockers, ACE inhibitors etc
Arthritis	Pain in the morning and more pain at night	NSAIDs, Glucocorticoids
Diabetes mellitus	Increase in the blood sugar level after meal	Sulfonylurea, Insulin, Biguanide
Attention	Increase in DOPA level in afternoon deficit syndrome	Methylphenidate
Hypercholesterolemia	Cholesterol synthesis is generally higher during night than during day time.	HMG CoA, reductase, inhibitors

Polymers used In Pulsatile Drug Delivery System

Pulsatile drug delivery systems are required. Pulsatile drug delivery systems are required for applications in which the continuous release of a drug would be detrimental and repeated dosing would be difficult, painful or otherwise problematic. A key example is insulin delivery for the treatment of diabetes. For effective management, insulin release levels need to be generally very low but significantly elevated after meals. Additional examples of the desirability of pulsatile drug delivery include the delivery of blood pressure medications and immunization boosters, and many hormone treatments. Pumps have been successfully used for pulsatile drug delivery and are now used for many diabetic patients. However, these suffer from a number of limitations, most notably the need to run tubing across the skin, which produces pathways for infection. Completely implantable systems would reduce this risk. The system proposed by Langer and co-workers exploits the wide tailor ability of biodegradation of the poly (lactic-co-glycolic acid) (PLGA) family of biocompatible polyesters. By varying the relative amounts of lactic acid and glycolic acid in the copolymer and

also the molecular weight of the copolymer, one can controllably and widely vary the degradation rate of the material. To release bursts of drug at different times, several PLGA copolymers with different degradation rates were used as 'gatekeepers'. Each copolymer was designed to hold back a burst of drug until that particular membrane had degraded sufficiently to allow the drug to escape. With this system, Langer and colleagues were able to achieve pulsatile release of several types of 'model drugs' with different properties. The drug-delivery system is based on a microchip formed from poly (L lactic acid), the most slowly degrading of this polyester family.

Several reservoirs were indented in the chip surface; drug solutions were microinjected into the appropriate reservoirs, and then PLGA membranes of various compositions were formed to seal each reservoir. Reservoirs could all contain the same drug, or multiple agents could be loaded into different reservoirs to release a variety of drugs from the device. One could envisage an implantable microchip that would release a battery of childhood immunizations at appropriate times. Such a system would be especially useful in developing

countries, where routine access to medical care is difficult and thus booster immunizations are often missed. Furthermore, because the drug molecules are stored in a reservoir rather than suspended in the polymer formulation, this system should be compatible with a wide variety of drugs. For example, heparin a common anti-coagulant that is hydrophilic bioactive after incorporation into and release from this drug delivery system, even after 140 days. The superb performance of this new device, along with the long track record for safety and biocompatibility of the polymer materials used to fabricate the device, bode well for success in a variety of clinical applications. The next advance in pulsatile drug delivery is likely to be systems in which release from an implant can be actively modulated, to increase or decrease dosing in response to demand. Ideally, such systems will eventually be coupled to biosensor devices so that drug delivery can respond to physiological cues in real time. The release of insulin from an implant could be tied to readings from a glucose sensor, thus providing tighter control over blood glucose levels and reducing the effects of diabetes. Drug release from polymeric systems could be controlled through externally generated the ultrasonic energy can be safely applied from outside the body and can be generated with a small, portable probe. In another example, composites of thermally responsive polymers with nanoparticles that absorb in the near infrared have been shown to undergo marked phase changes in response to near-infrared light. This might be useful as a drug delivery system that releases the drug upon external illumination from a light source similar in size to a laser pointer. These stimuli responsive systems are likely to offer greater control and flexibility than systems based on inherent differences in polymer degradation, but they will also be more complicated and costly. The potential benefits of pulsatile dosing regimens for a variety of conditions should ensure a high level of interest in modulated drug delivery systems well into the future, and advances in materials science will significantly improve our capabilities in this field of drug delivery.

Methods of Pulsatile Drug Delivery System

Currently Reported Systems

Pulsatile systems are basically time controlled drug delivery systems in which the system controls the lag time independent of environmental factors like pH, enzymes, gastro-intestinal motility, etc. These time controlled systems can be classified as

- Single unit (e.g., tablet or capsule) or
- Multiple unit (e.g., pellets, beads) systems.

Single-unit systems

- Capsular Systems
- Capsular System Based on Osmosis
- Pulsatile system with erodible or Soluble barrier coating
- Pulsatile system with Rupturable

Multiple-unit systems

- Pulsatile System Based on Rupturable Coating
- Osmotic-Based Rupturable Coating Systems
- Pulsatile system delivery by change in membrane permeability

Single-Unit Systems

Capsular systems

Different single-unit capsular pulsatile drug delivery systems have been developed. A general structure of such systems consists of an insoluble capsule body housing a drug and a plug. The plug is removed after a predetermined lag time owing to swelling, erosion or dissolution. The Pulsincap® system shown in Figure 4 (Scherer DDS, Ltd) 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 lag time. This is followed by a rapid drug release. The lag time can be controlled by manipulating the dimension and the position of the plug. For water-insoluble drugs, a rapid release can be ensured by inclusion of effervescent agents or disintegrants. 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, glyceryl monooleate), and enzymatically controlled erodible polymer (e.g., pectin). These formulations were well tolerated in animals and healthy volunteers, and there were no reports of gastrointestinal irritation. 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 intestine¹⁰.

Capsular System Based on Osmosis

The Port System shown in figure 5. Drug release mechanism from PORT system is shown in figure 6 (Port Systems, LLC) 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 in contact with the aqueous medium, water diffuses across the semi permeable membrane, resulting in increased inner pressure that ejects the plug after a lag time. The lag time is controlled by coating thickness. The system showed good correlation in lag times of invitro and in-vivo experiments in humans. The system was proposed to deliver methylphenidate for the treatment of attention deficit hyperactivity disorder (ADHD) in school-age children. Such a system avoids a second daily dose that otherwise would have been administered by a nurse during school hrs¹¹.

A System Based on Expandable Orifice

The system was designed to deliver drugs as liquid formulations and combine the benefits of extended release with high bioavailability. The liquid formulation is well suited for delivery of insoluble drugs, macromolecules such as polypeptides and polysaccharides. For delivery of such molecules a liquid environment favours solubilisation, dispersion, and protection from enzymatic degradation^{12, 13}. The Liquid OROS Softcap™ developed by Alza Corporation, USA, shown in figure 7 includes a liquid drug layer, an osmotic engine, push layer, and a semi permeable membrane coating. When the system is in contact with the aqueous environment, water permeates across the rate controlling membrane and activates the osmotic layer. The expansion of the osmotic layer results in the development of hydrostatic pressure inside the system, thereby forcing the liquid formulation to be delivered from

the delivery orifice as shown in figure 8. The Liquid OROS hard cap TM was framed to accommodate more viscous suspension with higher drug-loading capacity. The lag time can be delayed from 1 to 10 hrs, depending on the permeability of the rate-controlling membrane and thickness of the barrier layer. A variety of OROS systems have been developed using this technology such as Procardia XL, Ditropan XL, and Concerta.

Delivery by a Series of Stops

Pulsatile delivery by series of stops shown in fig.8. This system is described for implantable capsules. The capsule contains a drug and a water-absorptive osmotic engine that are placed in compartments separated by a movable partition. The pulsatile delivery is achieved by a series of stops along the inner wall of the capsule. These stops obstruct the movement of the partition but are overcome in succession as the osmotic pressure rises above a threshold level. The number of stops and the longitudinal placements of the stops along the length of the capsule dictate the number and frequency of the pulses, and the configuration of the partition controls the pulse intensity. This system was used to deliver porcine somatotropin¹⁴.

Pulsatile Delivery by Solubility Modulation

Such systems contain a solubility modulator for pulsed delivery of variety of drugs. The system was especially 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. Salbutamol has solubility of 275 mg/ml in water and 16 mg/ml in saturated solution of NaCl.

While NaCl has solubility of 321 mg/ml in water, and its saturation solubility is 320 mg/ml. These values show that the solubility of the drug is function of the modulator concentration, while the modulator's solubility is largely independent of drug concentration. The modulating agent can be a solid organic acid, inorganic salt, or organic salt. In order to control zero-order release period and commencement of pulsed release, ratio of drug/modulator can be varied. After the period of zero-order release, the drug is delivered as one large pulse. A similar system is described for delivery of terbutaline and oxprenolol. However, in general, the large-scale manufacturing of these systems is complicated and calls for special equipments and several manufacturing steps^{15, 16}.

Pulsatile system with erodible or soluble barrier coating

Most of the pulsatile drug delivery systems are reservoir devices coated with a barrier layer. This barrier erodes or dissolves after a specific lag period, and the drug is subsequently released rapidly. The lag time depends on the thickness of the coating layer figure 9. The time clock system shown in figure 10 (West Pharmaceutical Services Drug Delivery and Clinical Research Centre) consists of a solid dosage form coated with lipidic barriers containing carnauba wax and bees' wax along with surfactants, such as polyoxyethylene sorbitan monooleate. This coat erodes or emulsifies in the aqueous environment in a time proportional to the thickness of the film, and the core is then available for dispersion. In a study with human volunteers, it was shown that the lag time was independent of gastric residence time, and the hydrophobic film redispersion did not appear to be

influenced by the presence of intestinal enzymes or mechanical action of stomach or gastro-intestinal pH. The lag time increased with increasing coating thickness. Such systems are better suited for water soluble drugs. The major advantage of this system is its ease of manufacturing without any need of special equipment. However, such lipid-based systems may have high in-vivo variability (e.g., food effects)^{17, 18}. The possible problems of erosion controlled systems include a premature drug release when the penetrating water dissolves the drug, which diffuses out through the barrier layers, and sustained release after the lag phase when the barrier layer is not eroded or dissolved completely, thereby retarding the drug release. The Chronotropic system shown in figure 10 consists of a drug containing core coated by hydrophilic swellable hydroxyl propyl methyl cellulose (HPMC), which is responsible for a lag phase in the onset of release. In addition, through the application of an outer gastric-resistant enteric film, the variability in gastric emptying time can be overcome, and a colon-specific release can be obtained, relying on the relative reproducibility of small intestinal transit time. The lag time is controlled by the thickness and the viscosity grades of HPMC. The cores containing antipyrine as the model drug were prepared by tableting and retarding, and enteric coats were applied in a fluidized bed coater. The in-vitro release curves displayed a lag phase preceding drug release, and the in-vivo pharmacokinetic data showed a lag time prior to presence of detectable amounts of drug in saliva. Both in-vitro and in-vivo lag times correlate well with the applied amount of the hydrophilic retarding polymer. The system is suitable for both tablets and capsules^{19, 20}.

Multilayered Tablet

A release pattern with two pulses was obtained from a three-layered tablet containing two drug containing layers separated by a drug-free gellable polymeric barrier layer. This three-layered tablet was coated on three sides with impermeable ethyl cellulose, and the top portion was left uncoated. Upon contact with dissolution medium, the initial dose incorporated into the top layer was released rapidly from the noncoated surface. The second pulse was obtained from the bottom layer after the gelling barrier layer of HPMC was eroded and dissolved. The rate of gelling and/or dissolution of the barrier layer control the appearance of the second pulse. The gelling polymers reported include cellulose derivatives like HPMC, methyl cellulose, or polyvinyl alcohols of various molecular weights and the coating materials include ethyl cellulose, cellulose-acetate propionate, methacrylic polymers, acrylic and methacrylic co polymers, and polyalcohols^{21, 22}.

Pulsatile system with Rupturable coating

In contrast to the swellable or erodible coating systems, these systems depend on the disintegration of the coating for the release of drug. The pressure necessary for the rupture of the coating can be achieved by the effervescent excipients, swelling agents, or osmotic pressure figure 11. An effervescent mixture of citric acid and sodium bicarbonate was incorporated in a tablet core coated with ethyl cellulose. The carbon dioxide developed after penetration of water into the core resulted in a pulsatile release of drug after rupture of the coating. The release may depend on the mechanical properties of the coating layer. It is reported that the weak and non-flexible ethyl cellulose film ruptured sufficiently as compared to more flexible films. The

lag time increases with increasing coating thickness and increasing hardness of the core tablet. The highly swellable agents, also called super disintegrants, were used to design a capsule-based system comprising a drug, swelling agent, and rupturable polymer layer. Examples of superdisintegrants include cross carmellose, sodium starch glycolate, and low substituted hydroxypropyl cellulose. The swelling of these materials resulted in a complete film rupture followed by rapid drug release. The lag time is function of the composition of the outer polymer layer. The presence of hydrophilic polymer like HPMC reduced the lag time. The system can be used for delivery of both solid and liquid drug formulations. A reservoir system with a semi permeable coating was designed for delivery of drugs that exhibit extensive first-pass metabolism. The release pattern was similar to that obtained after administration of several immediate-release doses^{23,24}.

Advantage: Ease of manufacturing

Disadvantages: In-vivo variability (food effects which is present in G.I.T.)

Multiple - Unit Systems

Multiple systems (e.g., pellets, beads) offer various advantages over single unit systems. These include no risk of dose dumping, flexibility of blending units with different release patterns, and reproducible and short gastric residence time. But the drug carrying capacity of multiple systems is lower due to presence of higher quantity of excipients. Such systems are invariably a reservoir type with either rupturable or altered permeability coating.

Pulsatile System Based on Rupturable Coating Time-Controlled Explosion System

This is a multiple system in which drug is coated on non-pareil sugar seeds followed by a swellable layer and an insoluble top layer. The swelling agents used include superdisintegrants like sodium carboxymethyl cellulose, sodium starch glycolate, L-hydroxypropyl cellulose, polymers like polyvinyl acetate, polyacrylic acid, polyethylene glycol, etc. Alternatively, an effervescent system comprising a mixture of tartaric acid and sodium bicarbonate may also be used. Upon ingress of water, the swellable layer expands, resulting in rupture of film with subsequent rapid drug release. The release is independent of environmental factors like pH and drug solubility. The lag time can be varied by varying coating thickness or adding high amounts of lipophilic plasticizer in the outermost layer. A rap release after the lag phase was achieved with increased concentration of osmotic agent. In vivo studies of time-controlled explosion system (TCES) with an in-vitro lag time of three hours showed appearance of drug in blood after 3 hrs, and maximum blood levels after 5 hrs^{25,26}.

Osmotic-Based Rupturable Coating Systems Permeability Controlled System

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

large number of pellets consisting of two or more pellets or parts (e.g., populations). Each pellet has a core that contains the therapeutic drug and a water soluble osmotic agent. Water-permeable, water-insoluble polymer film encloses each core. A hydrophobic, water-insoluble agent that alters permeability (e.g., a fatty acid, wax, or a salt of fatty acid) is incorporated into the polymer film. The rate of water influx and drug efflux causes the film coating of each population to differ from any other pellet coating in the dosage form.

The osmotic agents dissolve in the water causing the pellets to swell, thereby regulating the rate of drug diffusion. The effect of each pellet population releasing its drug content sequentially provides a series of pulses of drug from a single dosage form. The coating thickness can be varied amongst the pellets. This system was used for the delivery of antihypertensive drug, diltiazem. The use of osmotically active agents that do not undergo swelling was reported by Schultz and Kleinbudde. The pellet cores consisted of drug and sodium chloride. These were coated with a semi-permeable cellulose acetate polymer. This polymer is selectively permeable to water and is impermeable to the drug. The lag time increased with increase in the coating thickness and with higher amounts of talc or lipophilic plasticizer in the coating. The sodium chloride facilitated the desired fast release of drug. In absence of sodium chloride, a sustained release was obtained after the lag time due to a lower degree of core swelling that resulted in generation of small fissures²⁷.

Pulsatile delivery system by change in membrane permeability

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

The ammonium group being hydrophilic facilitates the interaction of polymer with water, thereby changing its permeability and allowing water to permeate the active core in a controlled manner. This property is essential to achieve a precisely defined lag time. The cores were prepared using theophylline as model drug and sodium acetate. These pellets were coated using Eudragit RS30D (10% to 40% weight gain) in four different layer thicknesses. A correlation between film thickness and lag time was observed. It was found that even a small amount of sodium acetate in the pellet core had a dramatic effect on the drug permeability of the Eudragit film. After the lag time, interaction between the acetate and polymer increases the permeability of the coating so significantly that the entire active dose is liberated within a few minutes. The lag time increases with increasing thickness of the coat, but the release of the drug was found to be independent of this thickness and depended on the amount of salt present in the system²⁸.

Sigmoidal Release System

This consists of pellet cores comprising drug and succinic acid coated with ammonio-methacrylate copolymer USP/NF type B. The lag time is controlled by the rate of water influx through the polymer membrane. The water dissolves succinic acid and the drug in the core and the acid solution in turn

increases permeability of the hydrated polymer film. In addition to succinic acid, acetic acid, glutaric acid, tartaric acid, malic acid, or citric acid can be used. The increased permeability can be explained by improved hydration of film,

which increases free volume. These findings were used to design a coated delivery system with an acid containing core. The invitro lag time correlated well with in-vivo data when tested in beagle dogs^{29, 30}.

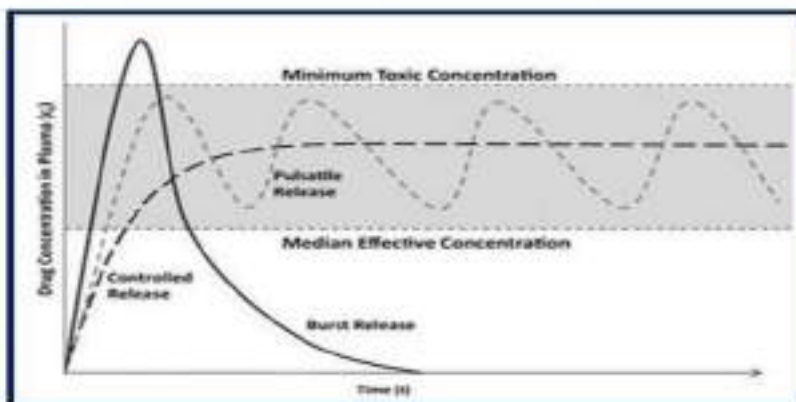


Figure 1: Plasma control drug release profile
Where, MEC=Minimum effective concentration, MSC=Minimum safe concentration
CRF=Controlled release formulation, CF=Conventional dosage formulation

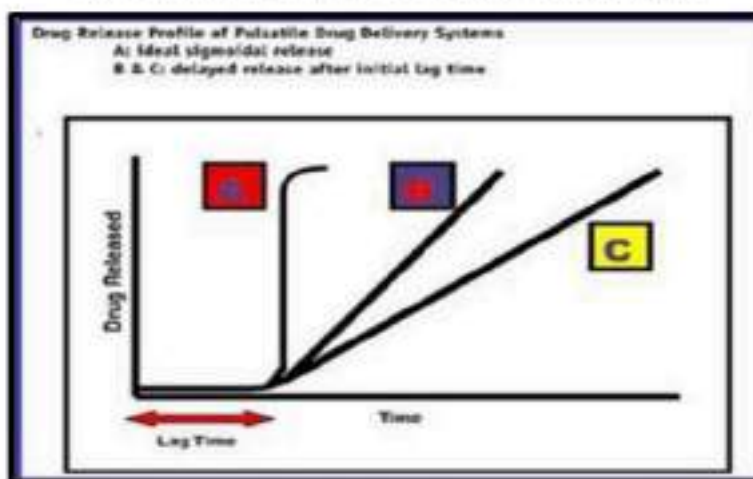


Figure 2: Drug release profile in pulsatile drug delivery system

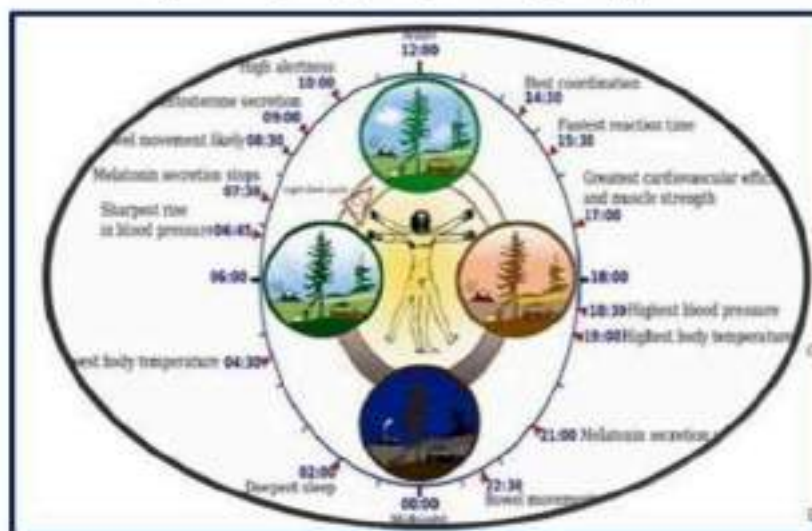


Figure 3: Cycle of Circadian rhythm

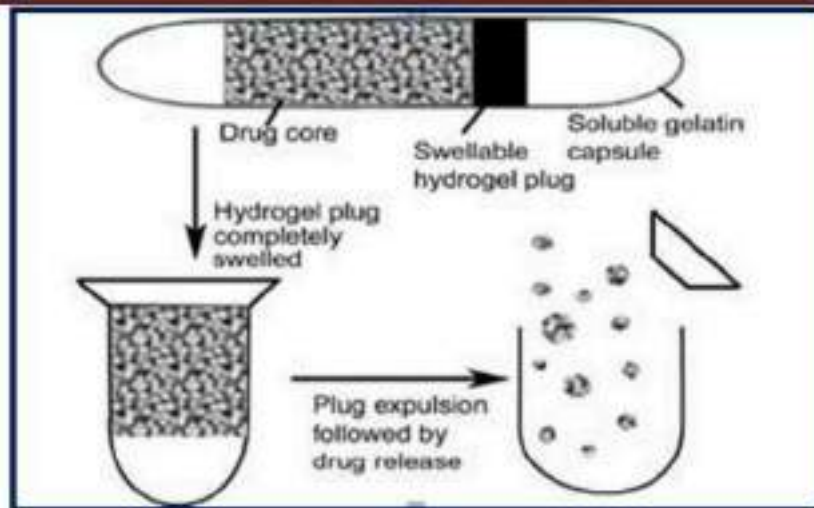


Figure 4: Design of Pulsinap system

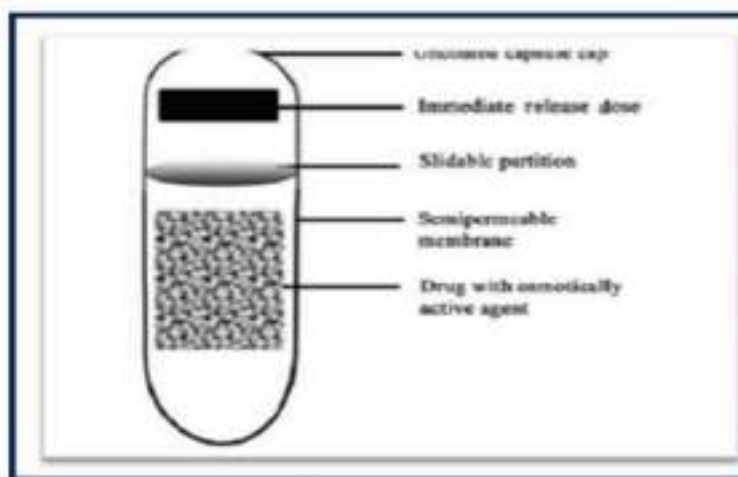


Figure 5: Plan of Port System

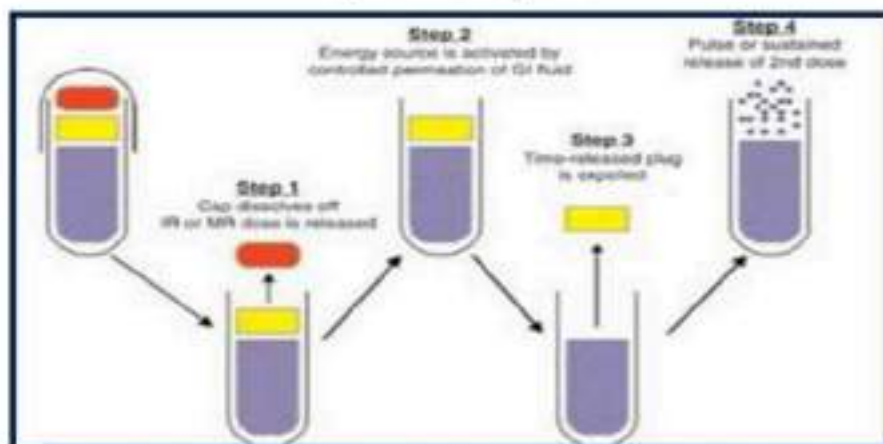


Figure 6: Drug release mechanism from Port

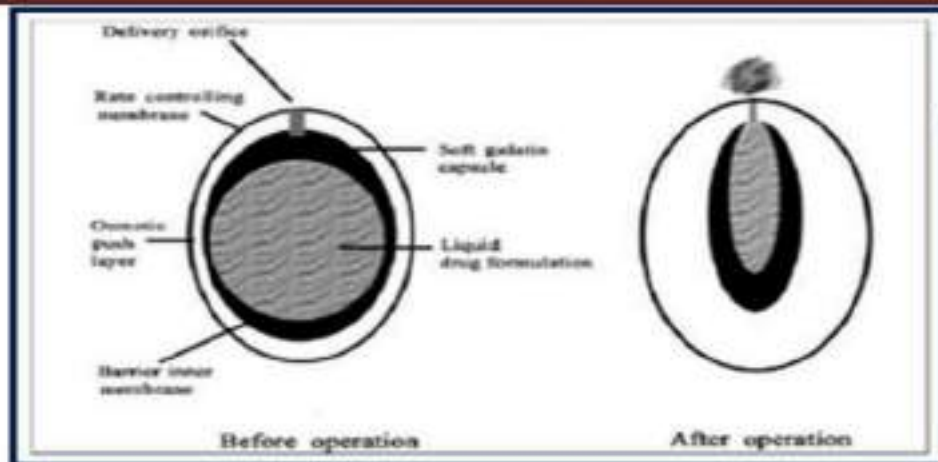


Figure 7: L-OROS Soft Cap system

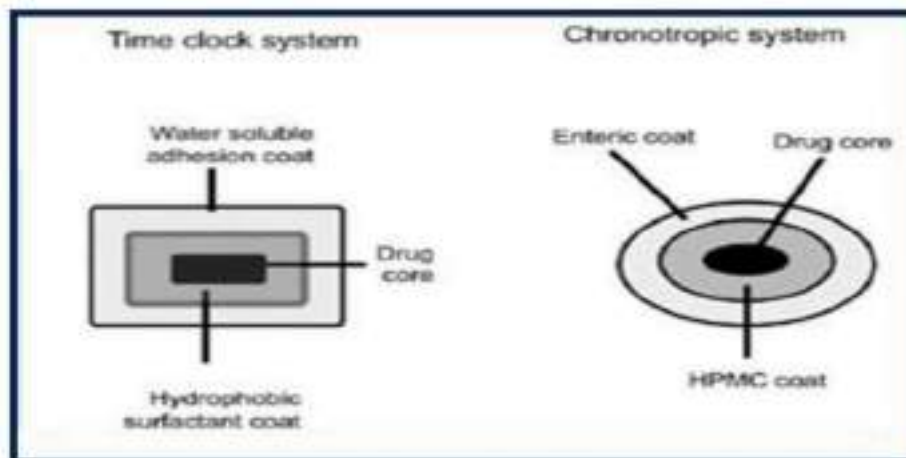


Figure 8: Time clock and Chronotropic systems

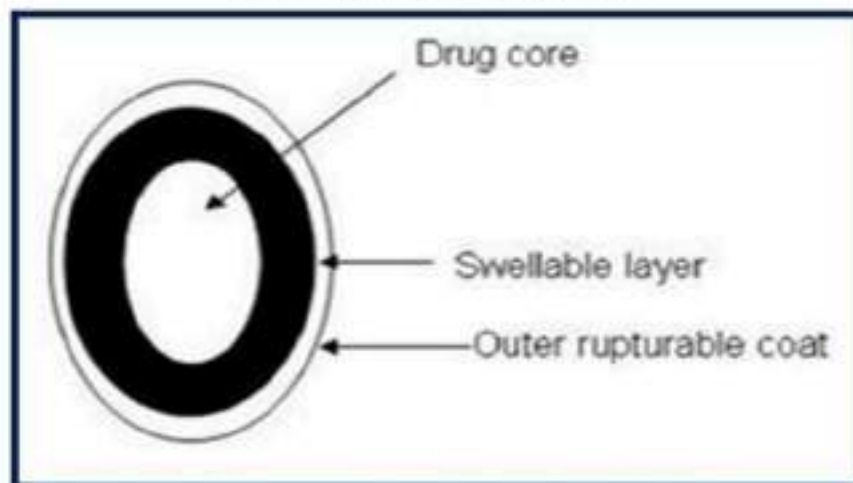


Figure 9: Schematic diagram of Delivery systems with rupturable coating layer

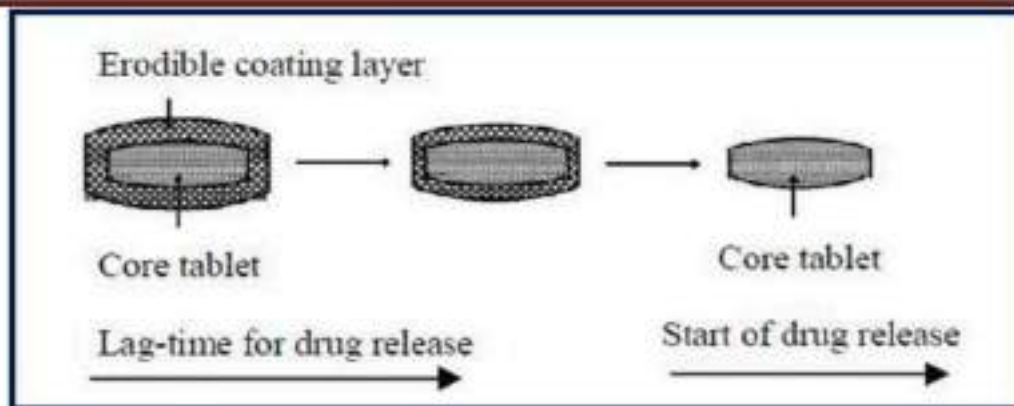


Figure 10: Schematic diagram of drug delivery with erodible coating layer

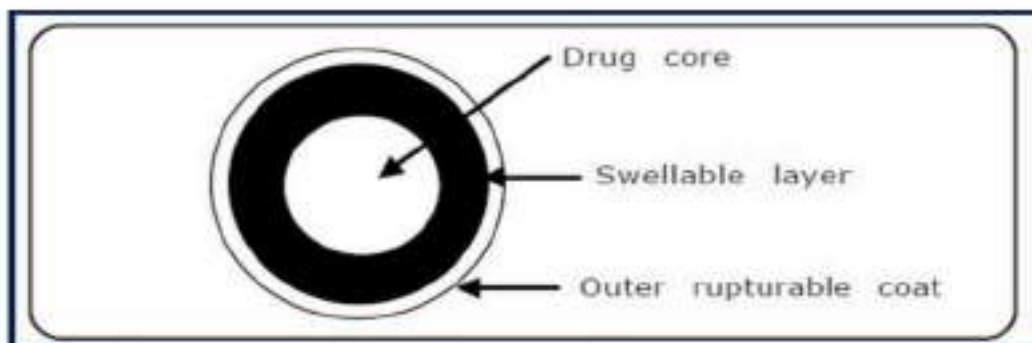


Figure 11: Schematic diagram of drug delivery with rupturable coating layer

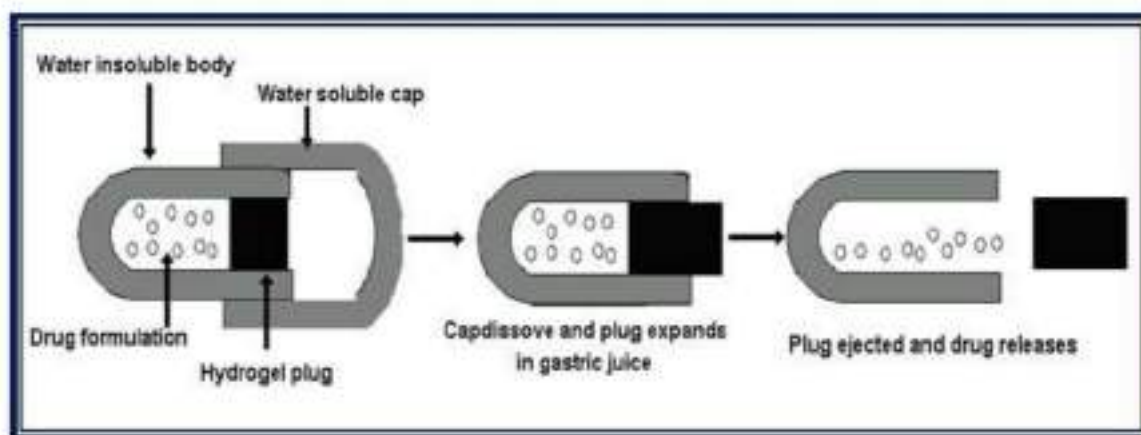


Figure 12: Schematic diagram of release of drug from capsule

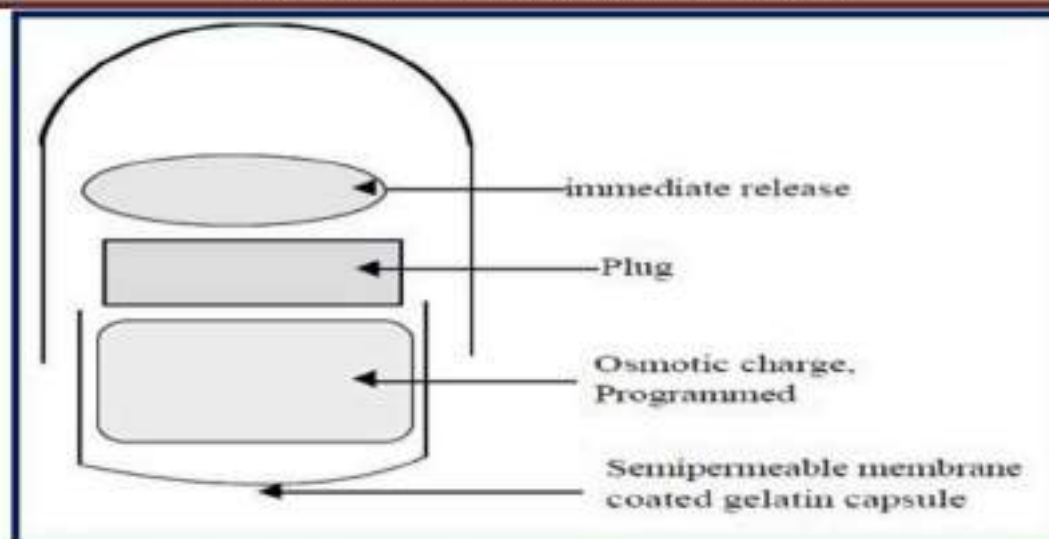


Figure 13: Schematic diagram of osmosis system

Formulation Consideration

Different approaches of pulsatile system are broadly divided as follows:

1. Time controlled,
2. Internal stimuli induced,
3. Externally regulated,
4. Multiparticulate.

Time controlled system

In time controlled drug delivery system, drug is released in pulsatile manner after specific time interval in order to coincide the drug with proper site, thus mimic the circadian rhythm^{31,32}.

Pulsatile Delivery by Solubilisation or Erosion of layer:

In such systems, the core containing drug is coated with the soluble or erodible polymer as outer coat and drug release is controlled by the dissolution or erosion of the outer coat. Time dependent release of the drug can be obtained by optimizing the thickness of the outer coat as shown in figure 12.

E.g. The Time Clock system^{33,34} and the Chronotropic system³⁵.

Pulsatile Delivery by Rupture of Membrane

In place of swelling or eroding, these systems are dependent 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 swelling, disintegrants, effervescent excipients, or osmotic pressure. Water permeation and mechanical resistance of the outer membrane are major factors affecting the lag time.

Capsule Shaped Pulsatile Drug Delivery System:

This dosage form consists of an insoluble capsule body containing a drug and swellable and degradable plugs made of approved substances such as hydrophilic polymers or lipids and release controlling plug between immediate release compartment and pulsed release compartment. On contact with aqueous fluids, the cap rapidly dissolves thereby releasing the immediate release component followed by pulsed release component. The length of plug decides lag time^{36,37}.

Pulsatile System Based On Osmosis

Osmotic system consists of capsule coated with the semipermeable membrane.

Inside the capsule there is an insoluble plug consisting of osmotically active agent and the drug formulation³⁸, e.g. The Port System³⁹.

Internal stimuli induced system

In these systems, the release of the drug takes place after stimulation by any biological factor like temperature, or any other chemical stimuli⁴⁰. Many of the polymeric delivery systems experience phase transitions and demonstrate marked swelling deswelling changes in response to environmental changes including solvent composition ionic strength, temperature, electric fields, and light⁴¹.

Temperature-induced pulsatile release

This deviation sometimes can act as a stimulus that triggers the release of therapeutic agents from several temperature responsive drug delivery systems for diseases accompanying fever. The temperature induced pulsatile/triggered drug delivery systems utilize various polymer properties, including the thermally reversible coil/globule transition of polymer molecules, swelling change of networks, glass transition and crystalline melting⁴²⁻⁴⁶.

Thermo responsive hydrogel systems

Thermo-responsive hydrogel systems employ hydrogels which undergo reversible volume changes in response to changes in temperature. These gels shrink at a transition temperature that is referred to the lower critical solution temperature (LCST) of the linear polymer. Thermo-sensitive hydrosensitive hydrogels have a certain chemical attraction for water, and therefore they absorb water and swell at temperatures below the transition temperature whereas they shrink or deswell at temperatures above the transition temperature by expelling water. Thermally responsive hydrogels and membranes have been extensively exploited as platforms for the pulsatile drug delivery⁴⁷.

Thermo responsive polymeric micelle systems

In this type, the gel system tightly stores targeted drug in the micelles and rapidly releases controlled amount of the drug

by switching on-off of external stimuli such as temperature or infrared laser beam.

Jianxiang Zhang, et al synthesized thermally responsive amphiphilic poly(N isopropylacrylamide) (PNIPAm)-grafted polyphosphazene (PNIPAm-g- PPP) by stepwise cosubstitution of chlorine atoms on polymer backbones with amino-terminated NIPAm oligomers and ethyl glycinate (GlyEt)⁴⁸. Diflunisal (DIF)-loaded micelles were prepared by dialysis method. In vitro release test at various temperatures was also performed to study the effect of temperature on the drug release profiles. Chemical stimuli induced pulsatile systems: In these systems, there is release of the drug after stimulation by any biological factor like enzyme, pH or any other chemical stimuli. In these systems, the polymer undergoes swelling or deswelling phase in response to chemical reaction with membrane, alteration of pH and Inflammation induce, release of drug from polymer by swelling the polymer.

Glucose-responsive insulin release devices

In a glucose-rich environment, such as the bloodstream after a meal, the oxidation of glucose to gluconic acid catalysed by glucose oxidase can lower the pH to approximately 5.8. 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 delivery⁴⁹. 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. Kazunori Kataoka, et al reported remarkable change in the swelling induced by glucose demonstrated for the gel composed of PNIPAAm with phenylboronic acid moieties. On-off regulation of insulin release from the gel achieved through a drastic change in the solute transport property as a result of the formation and disruption of the surface barrier layer of the Gel⁵⁰.

pH sensitive drug delivery system

pH-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 pH. Examples of pH dependent polymers include cellulose acetate phthalate, polyacrylates, sodium carboxy methyl cellulose.

Inflammation-induced pulsatile release

Physical or chemical stress, such as injury, broken bones, etc., initiates inflammation reactions, because of which hydroxyl radicals (OH) are produced from these inflammation-responsive cells. Yui et al. designed drug delivery systems based on the polymers which responded to the hydroxyl radicals and degraded in a limited manner. Yui and coworkers used hyaluronic acid (HA), in the body, HA is mainly degraded either by hydroxyl radicals or a specific enzyme, hyaluronidase. Degradation through hydroxyl radicals however, is usually dominant and rapid when HA is injected at inflammatory sites. Thus, they designed cross linked HA with ethylene glycol diglycidylether or polyglycerol polyglycidylether. Thus, a surface erosion type of degradation was achieved. Patients with inflammatory diseases, such as rheumatoid arthritis, can be treated using this type of system^{51,52}.

Drug release from intelligent gels responding to antibody concentration

Miyata et al. focused on the development of stimuli responsive cross linking structures into hydro gels. Special care was given to antigen-antibody complex formation as the cross-linking units in the gel, since specific antigen recognition of an antibody can provide the foundation for a new device fabrication. Using the difference in association constants between polymerized antibodies and naturally derived antibodies towards specific antigens, reversible gel swelling/deswelling and drug permeation changes could occur. Thus, biological stimuli responsive hydrogels were created^{53,54}.

Enzymatically-activated Liposome

Drug loaded liposomes was incorporated into microcapsules of alginate hydrogels. Liposomes inside the microcapsules were coated with phospholipase A2 to achieve a pulsatile release of drug molecules. Phospholipase A2 was shown to accumulate at the water/liposome interfaces and remove an acyl group from the phospholipids in the liposome. Destabilised liposomes release their drug molecules, thus allowing drug release to be regulated by the rate determining microcapsule membrane^{55,56}.

Externally regulated pulsatile release system

This system is not self-operated, but instead requires externally generated environmental changes to initiate drug delivery. These can include magnetic fields, ultrasound, electric field, light, and mechanical force.

Magnetic induces release

Magnetic carriers receive their magnetic response to a magnetic field from incorporated materials such as magnetite, iron, nickel, cobalt etc. Magnetic-sensitive behavior of intelligent ferrogels for controlled release of drug was studied by Tingyu Liu, et al. An intelligent magnetic hydrogel (ferrogel) was fabricated by mixing poly (vinyl alcohol) (PVA) hydrogels and Fe₃O₄ magnetic particles through freezing-thawing Cycles⁵⁷. Although the external direct current magnetic field was applied to the ferrogel, the drug got accumulated around the ferrogel, but the accumulated drug spurt to the environment instantly when the magnetic fields instantly switched "off". Furthermore, rapid slow drug release can be tunable while the magnetic field was switched from "off" to "on" mode. The drug release behavior from the ferrogel is strongly dominated by the particle size of Fe₃O₄ under a given magnetic field⁵⁸. Tingyu Liu, et al developed the magnetic hydrogels which was successfully fabricated by chemically cross-linking of gelatin hydrogels and Fe₃O₄ nanoparticles (ca. 40-60 nm) through genipin (GP) as cross-linking agent⁵⁹.

Ultrasound induces release

Ultrasound is mostly used as an enhancer for the improvement of drug permeation through biological barriers, such as skin. The interactions of ultrasound with biological tissues is divided into two broad categories: thermal and non-thermal effects. Thermal effects are associated with the absorption of acoustic energy by the fluids or tissues⁶⁰. Non-thermal bio-effects are generally associated with oscillating or cavitating bubbles, but also include non cavitation effects such as radiation pressure, radiation torque, and acoustic streaming.

Electric field induces release

Electrically responsive delivery systems are prepared by polyelectrolytes (polymers which contain relatively high concentration of ionisable groups along the backbone chain) and are thus, pH-responsive as well as electro-responsive. Under the influence of electric field, electro-responsive hydrogels generally bend, depending on the shape of the gel which lies parallel to the electrodes whereas deswelling occurs when the hydrogel lies perpendicular to the electrodes. An electro responsive drug delivery system was developed by R. V. Kulkarni, et al., using poly(acrylamide-grafted-xanthan gum) (PAAm-g- XG) hydrogel for transdermal delivery of ketoprofen⁶¹.

Light induces release

Light-sensitive hydrogels have potential applications in developing optical switches, display units, and ophthalmic drug delivery devices⁶². The interaction between light and material can be used to modulate drug delivery. When hydrogel absorb the light and convert it to heat, raising the temperature of composite hydrogel above its LCST⁶³, hydrogel collapses and result in an increased rate of release of soluble drug held within the matrix.

Multiparticulate system

Recent trends indicate that multiparticulate drug delivery systems are especially suitable for achieving controlled or delayed release oral formulations with low risk of dose dumping, flexibility of blending to attain different release patterns as well as reproducible and short gastric residence time. Such systems are reservoir type with either rupturable or altered permeability coating and generally housed in capsular body. The purpose of designing multiparticulate dosage form is to develop a reliable formulation that has all the advantages of a single unit formulation and yet devoid of the danger of alteration in drug release profile and formulation behavior due to unit to unit variation⁶⁴.

Hypothetical design of a multiparticulate pulsatile system

Andrei Dashevsky, et al. developed a pulsatile multiparticulate drug delivery system (DDS), coated with aqueous dispersion of Aquacoat ECD. A rupturable pulsatile drug delivery system consists of (i) a drug core; (ii) a swelling layer, comprising a super disintegrant and a binder; and (iii) an insoluble, water-permeable polymeric coating⁶⁵. Upon water ingress, the swellable layer expands, resulting in the rupturing of outer membrane with subsequent rapid drug release. Regarding the cores, the lag time was shorter; theophylline was layered on sugar cores compared with cores consisting of theophylline. Regarding swelling layer, the release after lag time was fast and complete. Drug release was achieved after the lag time, when low-substituted hydroxypropyl cellulose (L-HPC) and sodium starch glycolate (Explotab) were used as swelling agents. Outer membrane, formed using aqueous dispersion Aquacoat® ECD was brittle and ruptured sufficiently to ensure fast drug release, compared to ethylcellulose membrane formed using organic solution. The addition of talc led to increase brittleness of membrane and was very advantageous. Drug release starts only after rupturing of outer membrane. C. Sun, et al. developed novel pH sensitive copolymer microspheres containing methyl acrylic acid and styrene cross-linking with divinylbenzene were synthesized by free radical polymerization. The copolymer microspheres showed pulsatile swelling behavior when the pH of the media

changed. The pH sensitive microspheres were loaded with diltiazem hydrochloride (DH)⁶⁶. The release characteristics of the free drug and the drug-loaded microspheres were studied under both simulated gastric conditions and intestinal pH conditions. The in vivo evaluation of the pulsatile preparation was subsequently carried out using beagle dogs. Sigmoidal Release System: This consists of pellet cores containing drug and succinic acid coated with ammoniomethacrylate copolymer USP/NF type B⁶⁷. The lag time is controlled by the rate of water influx through the polymer membrane. The water dissolves succinic acid, and the drug in the core and the acid solution in turn increases permeability of the hydrated polymer film. In addition to succinic acid, acetic acid, glutaric acid, tartaric acid, malic acid, or citric acid can be used. The increased permeability can be explained by improved hydration of film, which increases free volume. These findings were used to design a coated delivery system with an acid containing core^{68,69}. The in-vitro lag time correlated well with in-vivo data when tested in beagle dogs⁷⁰.

CONCLUSION

Presently, oral delivery of drug is still by far the most preferable route of drug delivery due to the ease of administration, patient compliance and flexibility in its formulations. Generally, sustained and controlled-release products provide a desired therapeutic effect, but fall short of diseases following biological rhythms. Circadian disorders such as hypertension, osteoarthritis, asthma etc. which require chronopharmacotherapy. PDDS can effectively tackle this problem as it is modulated according to body's circadian clock giving release of drug after a specified time lag. However, for the last two decades, technologies to ensure time-controlled pulsatile release of bioactive compounds have been developed. A significant progress has been made toward achieving PDDS that can effectively treat diseases with non-constant dosing therapies. Various pulsatile technologies are researched and some are currently in the market.

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