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PULSATILE DRUG DELIVERY SYSTEM: DRUG DELIVERY IN SYMPHONY WITH CIRCA-DIAN RHYTHM

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Keywords:
Pulsatile drug release; Lag time; Chronopharmacotherapy; Circadian rhythm, Capsular systems; Rupturable and Erodible system

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ABSTRACT

Pulsatile drug delivery system are gaining a lot of acceptance to deliver the drug at the right time and in the right amount, thus providing spatial and temporal delivery and increasing patient compliance. These systems are designed according to the circadian rhythm of the body. According to latin literature *Circa* means Day and *Dian* means night. This drug delivery system, is programmed drug delivery system in harmonization with body clock. The pulse has to be designed in such a way that a complete and rapid dug release is achieved after the lag time. Various system like capsular systems, osmotic system, 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 article. It summarizes the latest technological developments, formulation parameters, and release profiles of these systems. These systems are beneficial for the drugs having chronopharmacological behavior where night time dosing is required, such as anti-arrhythmic and anti-asthmatic.

Introduction

Controlled drug delivery systems have acquired a center stage in the area of pharmaceutical R&D business. Such systems control over the release of drug and grant a new lease on life to a drug molecule in terms of patentability. Oral controlled drug delivery systems represent the most popular form of controlled drug delivery systems for the obvious advantages of oral route of drug administration. Such systems release the drug with constant or variable release rates.[1] These dosage forms offer many advantages, such as nearly constant drug level at the site of action, prevention of peak-valley fluctuations, reduction in dose of drug, reduced dosage frequency, avoidance of side effects, and improved patient compliance.[2]

Oral controlled drug delivery system represent the most popular form of controlled drug delivery systems for the obvious advantages of oral route of drug administration. Such systems release the drug with constant or variable release rates. 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.[3]

Pulsatile Drug Delivery Systems

The principle rationale for the use of pulsatile release is for the drugs where a constant drug release, i.e., a zero-order release is not desired. Pulsatile drug delivery system is defined as the rapid and transient release of certain amount of molecules within a short time period immediately after a predetermined off-release period, i.e., lag time shown in figure 2 .Various systems like capsular systems, osmotic systems, Pulsatile system based on the use of soluble or erodible polymer coating, use of rupturable membranes and pulsatile system based on membrane permeability are summarized in this article. These systems are beneficial for the drugs having chronopharmacological behavior where night time dosing is required and for the drugs having high first-pass effect and having specific site of absorption in gastrointestinal tract.[4]

Why we need of Pulsatile drug delivery system?

Circadian rhythm

Pulsatile drug delivery system is the most interesting time- and site-specific system. This system is designed for chronopharmacotherapy which is based on circadian rhythm shown in figure 3. Thorough understanding of the disease physiology is required before designing the pulsatile drug delivery system. A disease where rhythmic circadian organization of the body plays an important role, pharmacokinetics and/or pharmacodynamics of the drugs is not

constant within 24 h. Table 1.Enumerates various diseases showing such a chronological behavior. Asthma is one such disease where pulsatile drug delivery system can be useful. Circadian changes are seen in normal lung function, which reaches a low point in the early morning hours. In case of 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.[5] Circadian variations of glucose and insulin in diabetes have been extensively studied and their clinical importance in case of insulin substitution in type 1 diabetes has been well exploited. Furthermore diverse directions of circadian changes in lipid fractions in patients and normal subjects may contribute to alteration in the rhythmicity of other metabolisms and in the blood coagulation system, thus leading to various complications. A circadian rhythm occurs during hepatic cholesterol synthesis. In case of arthritis there is a circadian rhythm in the plasma concentration of C-reactive protein and interleukin-6 of patients with rheumatoid arthritis.[6]

Merits of Pulsatile drug delivery system

1. Extended daytime or nighttime activity.
2. Reduced side effects.
3. Reduced dosage frequency.
4. Reduction in dose size.
5. Improved patient compliance.
6. Lower daily cost to patient due to fewer dosage units are required by the patient in therapy.
7. Drug adapts to suit circadian rhythms of body functions or diseases.
8. Drug targeting to specific site like colon.
9. Protection of mucosa from irritating drugs.
10. Drug loss is prevented by extensive first pass metabolism.[7]

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.

METHOD OF PULSATILE DRUG DELIVEY SYSTEM

SINGLE-UNIT SYSTEMS

1) Capsular Systems
2) Capsular System Based on Osmosis
3) Pulsatile system with erodible or Soluble barrier coating
4) Pulsatile system with Rupturable

MULTIPLE-UNIT SYSTEMS

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

1) 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 gastro-intestinal 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 intestine (Binnas et al., 1996). [8-9]

2) 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 semipermeable 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 semipermeable 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 *in-vitro* 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 hours. [10]

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 favors solublization, dispersion, and protection from enzymatic degradation.[11-12]

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 semipermeable 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 4. The Liquid OROS hardcap ™ was framed to accommodate more viscous suspension with higher drug-loading capacity. The lag time can be delayed from 1 to 10 h, 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 figure 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 somatotropin.[13]

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.[14-15]

a) **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(shown in figure 9).

The Time Clock® system shown in figure 10(West Pharmaceutical Services Drug Delivery & 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).[16-17]

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 hydroxypropylmethyl 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 tabletting 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.[18-19]

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 in 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 non-coated 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.[20-21]

b) 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 (shown in 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 glycollate, 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.[22-23]

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.

1) 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 glycollate, 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 rapid 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 hours, and maximum blood levels after 5 hours.[24-25]

2) 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 Kleinebudde. 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 fissures. [26]

3) 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 system. [27]

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 *in-vitro* lag time correlated well with *in-vivo* data when tested in beagle dogs. [28-29]

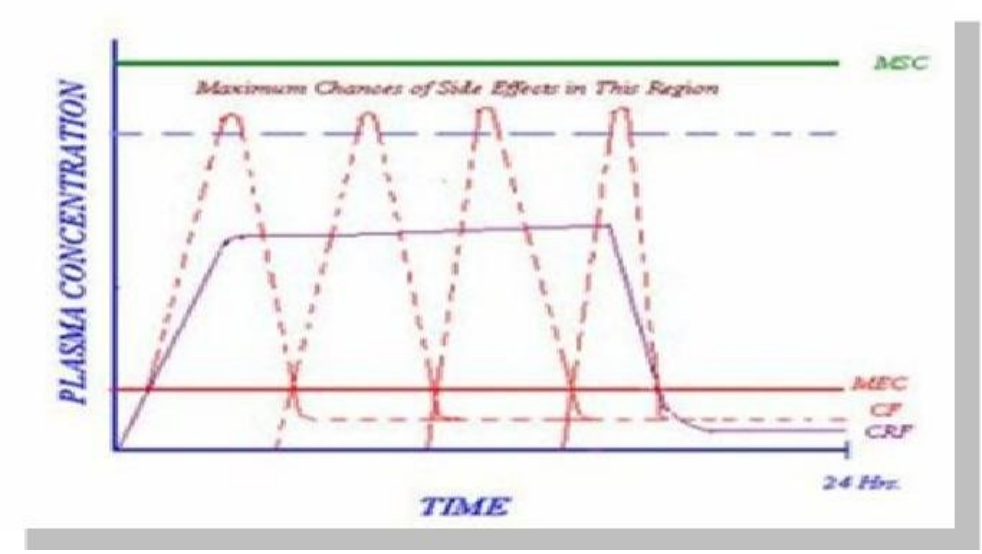
Merits:

1. Short gastric residence time
2. Reproducible gastric residence time
3. No risk of dose dumping
4. Flexible to blend pellets with different composition or release pattern
5. Lowest transit time variability
6. Unique profiles
7. Amenable to capsule & tablets

8. Capable of pulsatile release

Demerits :

1. Multiple manufacturing steps
2. Low drug load
3. Incomplete release



Where,

MEC=Minimum effective concentration

MSC=Minimum safe concentration

CRF=Controlled release formulation

CF=Conventional dosage formulation

Fig 1. Plasma control drug release profile

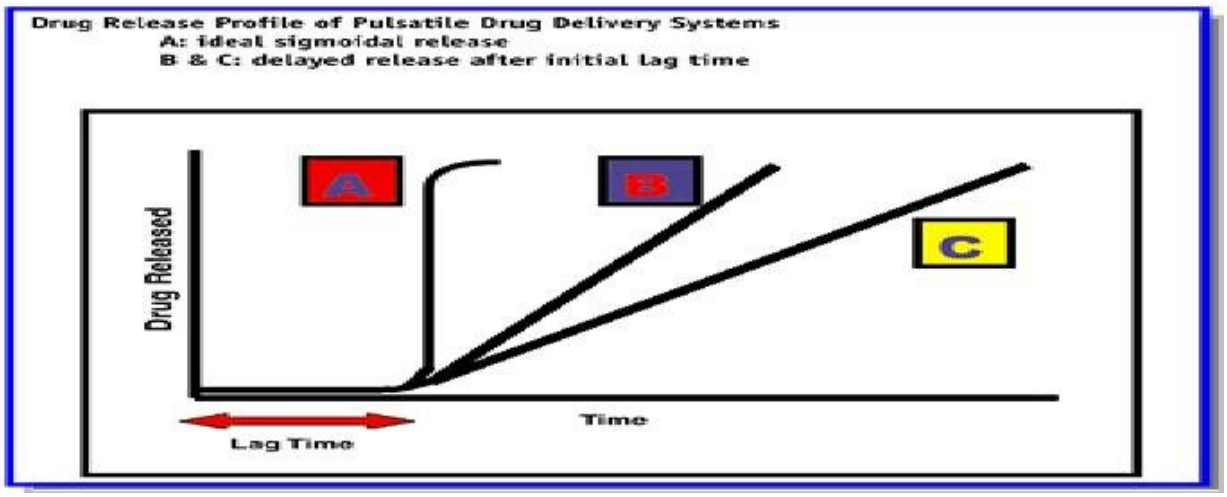


Fig. 2 Drug release profile in Pulsatile drug delivery system

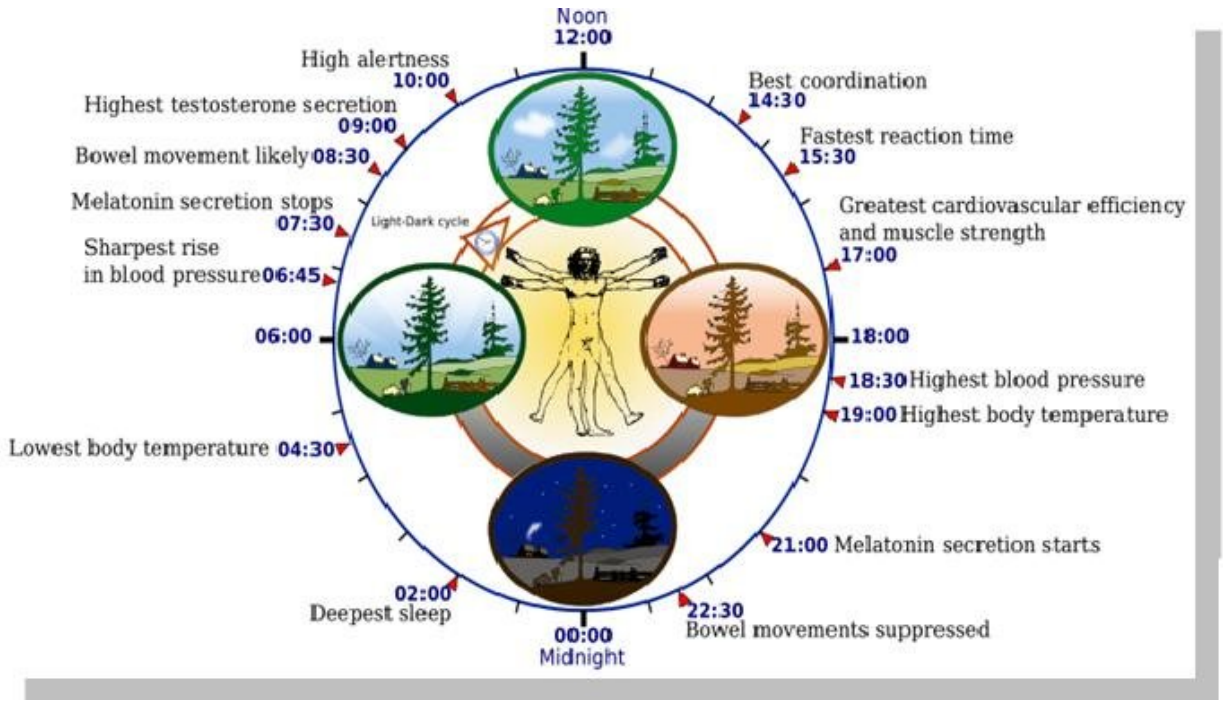


Fig 3. Cycle of Circardian rhythm

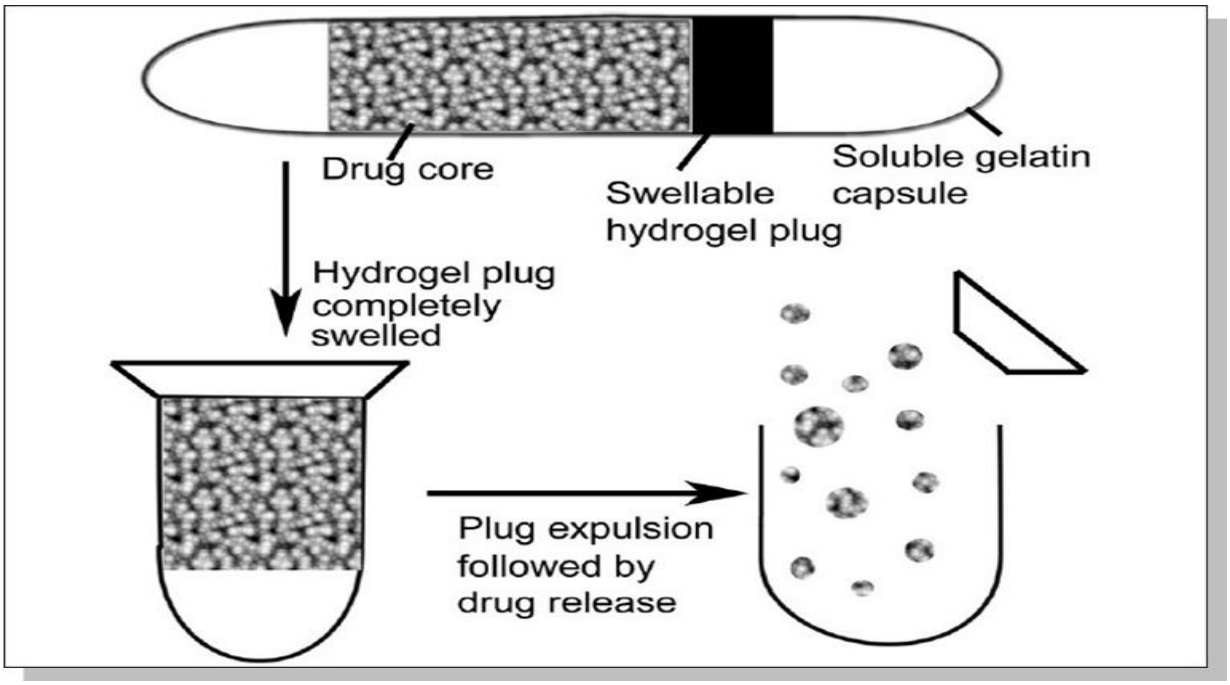


Fig 4. Design of Pulsincap® system

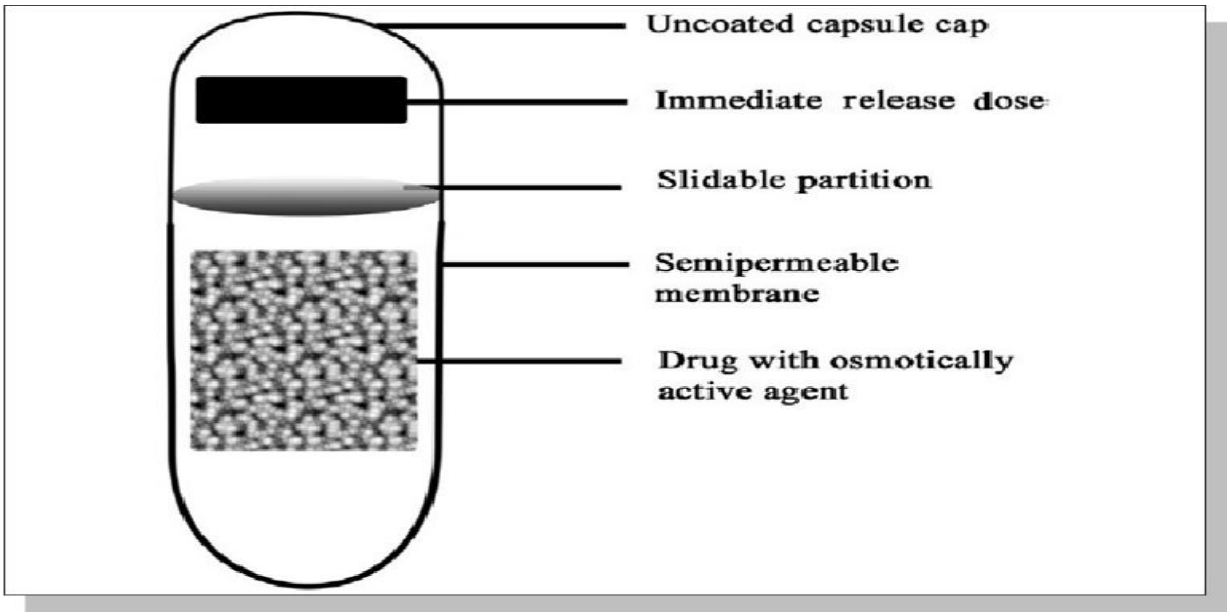


Fig 5. Plan of Port® System

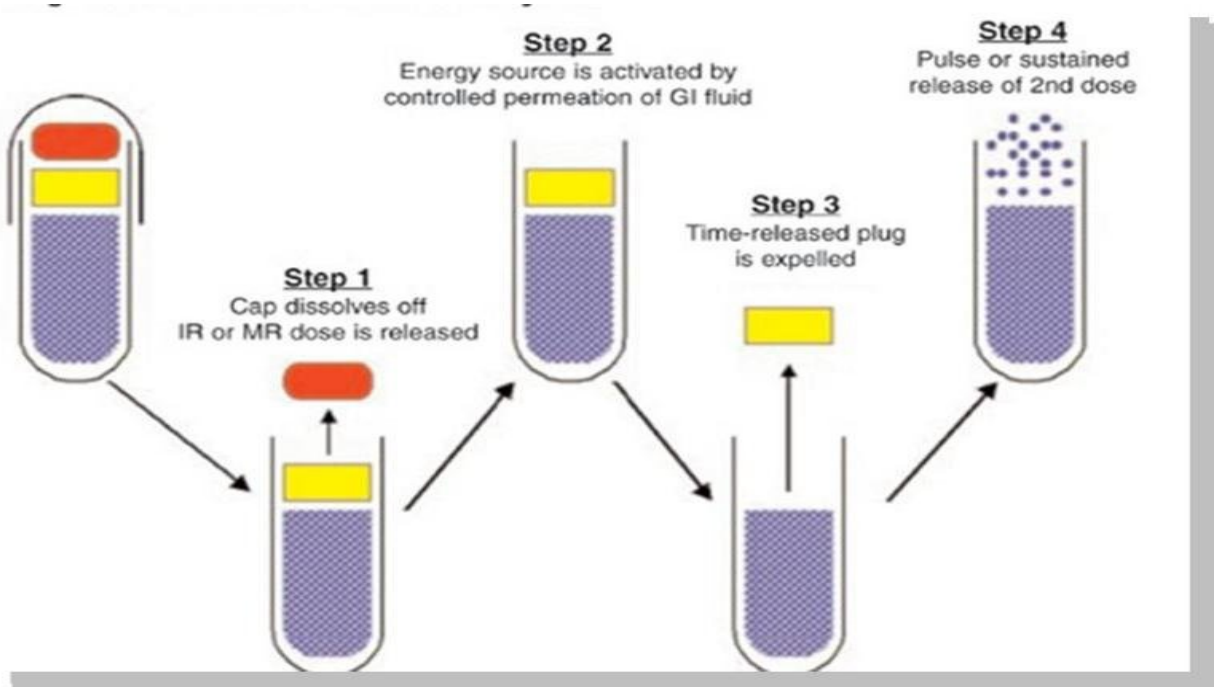


Fig 6. Drug release mechanism from Port®

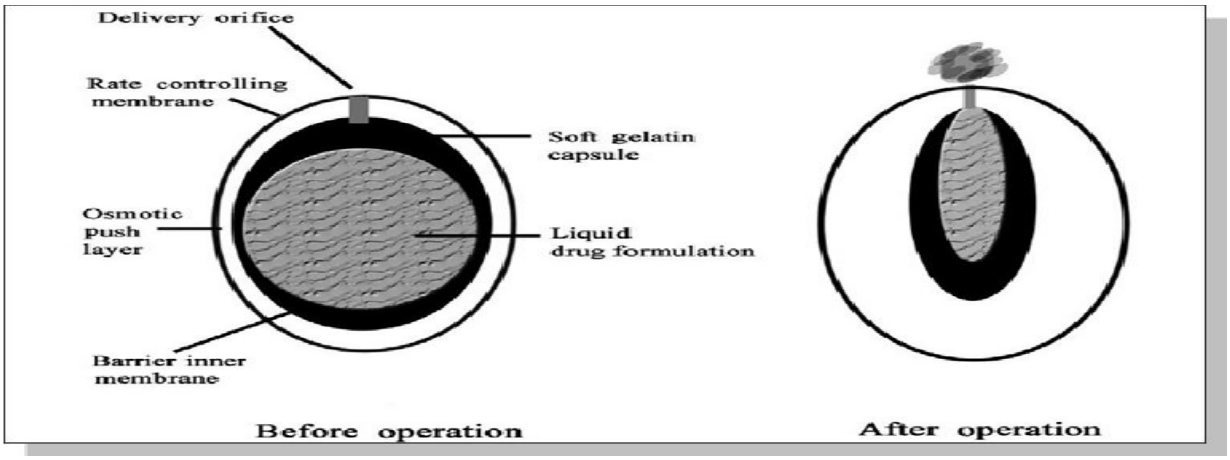


Fig 7. L-OROS Softcap system

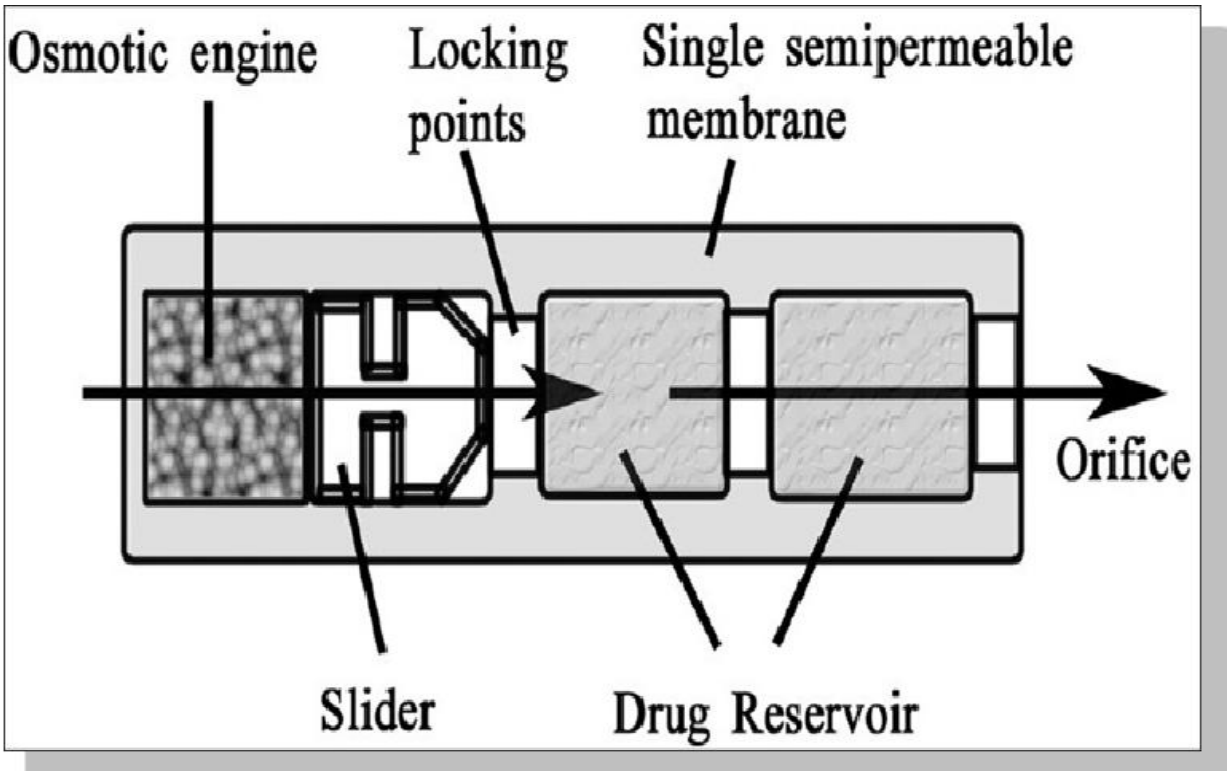


Fig 8. Pulsatile delivery by series of stops

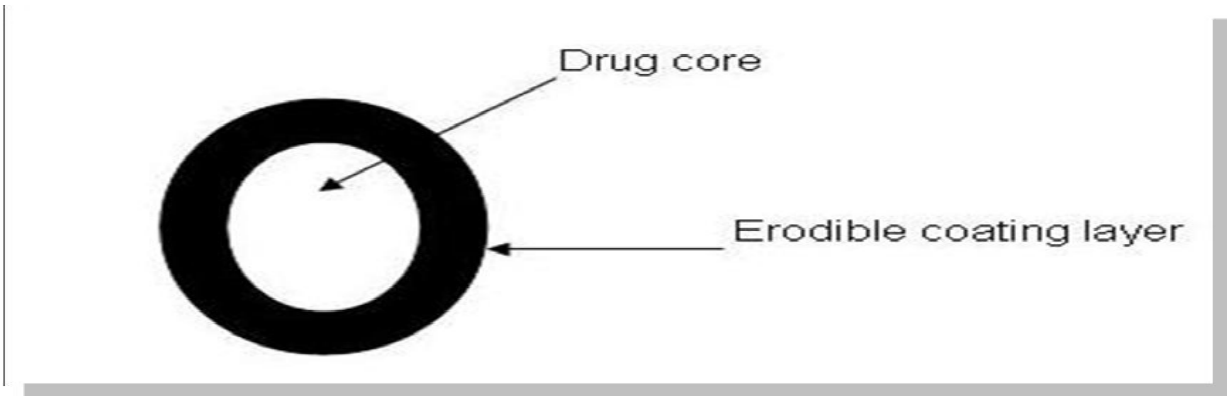


Fig 9. **Schematic diagram of Delivery systems with erodible coating layer**

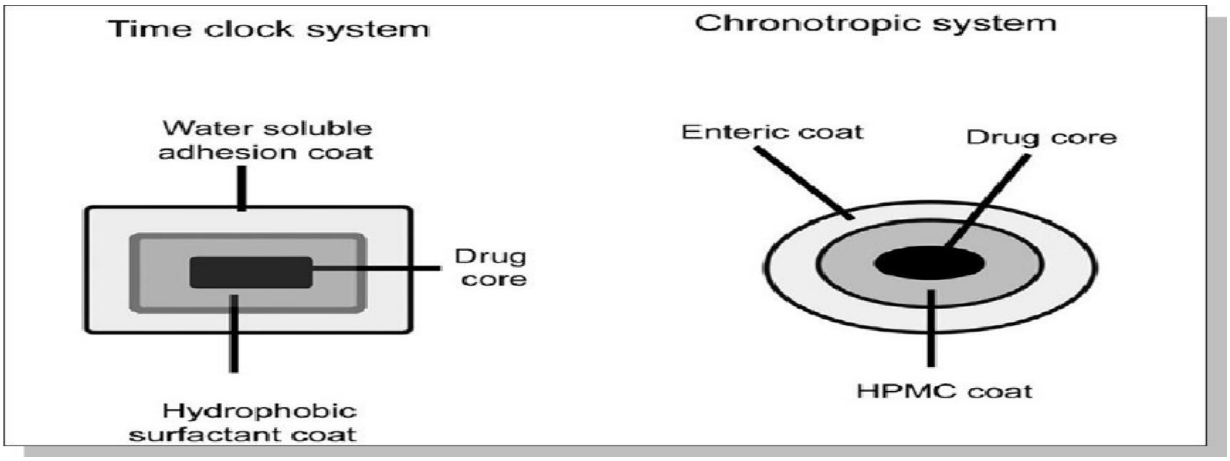


Fig 10. Time clock and Chronotropic systems

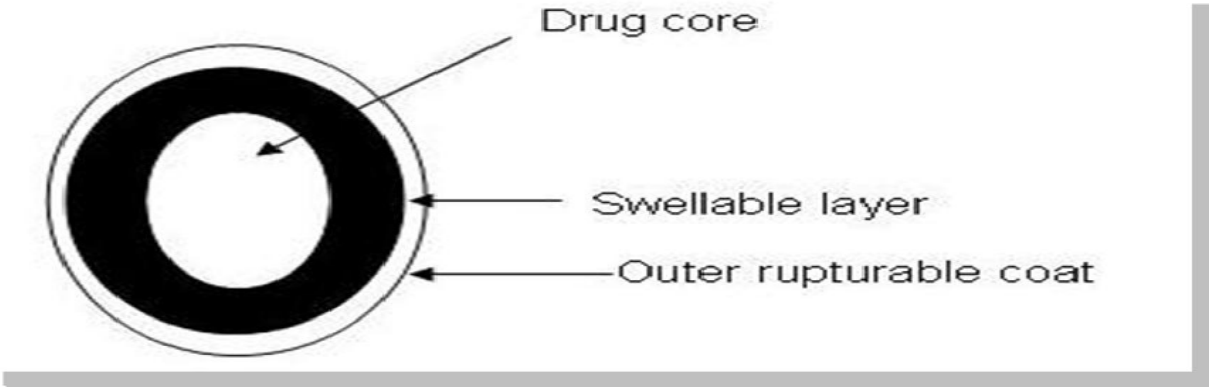


Fig 11. Schematic diagram of Delivery systems with rupturable coating layer.

Table 1. Diseases requiring Pulsatile Drug Delivery

Diseases	Chronological behavior	Drug used
Peptic ulcer	Acid secretion is high in the afternoon and at night	H_2 BLOCKERS
Asthma	Precipitation of attacks during the early morning awakening period	β_2 agonist, Antihistaminics

Cardiovascular diseases	BP is as its lowest during the sleep cycle and rise steeply during the early morning awakening period	Nitroglycerine, Calcium channel blocker, ACE inhibitors etc.
Artharitis	Pain in morning and more at night	NSAIDS, Glucocorticoids
Diabetes mellitus	Increase in the blood sugar level after meal	Sulfonylurea, Insulin, Biguanide
Attention deficit syndrome	Increase in DOPA level in afternoon	Methylphenidate
Hypercholesterolemia	Cholesterol synthesis is generally higher during night than during day time	HMG CoA reductase inhibitors

Table 2. Marketed Technologies of Pulsatile drug delivery

Technology	Mechanism	Proprietory name and Dosage form	API	Diseases

OROS®	Osmatic mechanism	Covera-HS ®: XL Tablet	Verapamil HCL	Hypertension
Three dimensional printing®	Externally regulated system	Theirform®	Dicloenac sodium	Inflammation
CODAS®	Multiparticular pH dependent system	Verelan® PM : XL release capsule	Verapamil HCL	Hypertension
DIFFUCAPS®	Multiparticular system	Innopran® : XL Tablet	Verapamil HCL;Propranolol HCL	Hypertension
PULSINCAP®	Rupturable system	Pulsincap®	Dofetilide	Hypertension

Polymer used in Pulsatile drug delivery system

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.[30]

Current and future Aspects:

Pulsatile-release formulations have many advantages over immediate-release formulations. With these formulations, less-frequent drug administration is possible, and patient compliance can correspondingly be improved. In the field of drug delivery, increased attention has recently been focused on the potential of systems that are able to release drugs after a programmable lag phase commencing at administration time, i.e., in a pulsatile mode. During the last two decades, technologies to ensure time-controlled pulsatile release of bioactive compounds have been developed. Significant progress has been made towards achieving pulsatile drug delivery systems that can effectively treat diseases with non-constant dosing therapies, such as diabetes. However, there is much work that needs to be carefully demonstrated for the pulsatile delivery of bioactive compounds, especially hormones.

Conclusion:

Oral drug delivery is the largest, oldest, and most preferred route of drug delivery. Universally sustained and controlled-release products provide a desired therapeutic effect, but fall for diseases following biological rhythms. Circadian disorders such as asthma, osteoarthritis, RA, cholesterol synthesis, etc., require chronopharmacotherapy. Pulsatile drug delivery can effectively crack this problem as it is modulated according to body's circadian clock giving release of drug after a specified lag time. During 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 Pulsatile drug delivery system that can effectively treat diseases with non-constant dosing therapies. Various pulsatile technologies are researched and brought in the market, which surely assure a bright and promising future.

References

1. Gennaro AR, ed. Remington: The Science and Practice of Pharmacy. 20th ed. USA: Lippincott, Williams & Wilkins; 2000;20:903-905.
2. Bussemer T, Otto I, Bodmeier R. Pulsatile drug delivery systems. Crit Rev Ther Drug Carrier Syst. 2001;18(5):433-58. Review.
3. Das NG, Das SK. Controlled release of oral dosage forms, formulation, finish, and fill. www.pharmtech.com. 2003; 10-16.
4. Kikuchi A, Okano T. Pulsatile drug release control using hydrogels. Adv Drug Deliv Rev 2002; 54:53-77.
5. Hermida RC, Ayala DE, Calvo C, et al. (2007) Adv.
6. Lemmer (1991) J. Control. Rel. 16:63-74
7. Umang Pharmatech Pvt. Ltd., Umang offers Road to Pelletisation through spher'odization. Express Pharma Pulse, 2000.
8. McNeil ME, Rashid A, Stevens HNE. Dispensing Device. WO Patent No. 90/09168 (1990).
9. Saeger H, Virley P. Pulsincap& Mac226: Pulsed-Release Dosage Form. Product information from Scherer DDS, Ltd; 2004.
10. Crison JR, Siersma PR, Amidon GL. A novel programmable oral release technology for delivering drugs: human feasibility testing using gamma scintigraphy. Proceed Intern Symp Control Rel Bioact Mater. 1996;23:51-52.
11. Pollock-Dove C, Dong L, Wong P. A new system to deliver a delayed bolus of liquid drug formulation. Proceed Intern Symp Control Rel Bioact Mater. 2001;28:6033.
12. Linkwitz A, Magruder JA, Merrill S. Osmotically Driven Delivery Device with Expandable Orifice for Pulsatile Delivery Effect. US Patent No. 5,318,558; 1994.
13. Balaban SM, Pike JB, Smith JP, Baile CA. Osmotically Driven Delivery Devices with Pulsatile Effect. US Patent No. 5209746; 1993.

14. Magruder PR, Barclay B, Wong PSL, Theeuwes F. Composition Comprising Salbutamol. US Patent No. 4751071; 1988.

15. Magruder PR, Barclay B, Wong PSL, Theeuwes F. Composition Comprising a Therapeutic Agent and a Modulating Agent. US Patent No. 4851229; 1989.

16. Pozzi F, Furlani P. Orale Feste Pharmazeutische Darreichungsform Mit Programmierter Freisetzung. DE Patent No. 4122039; 1992.

17. Wilding IR, Davis SS, Pozzi F, Furlani P, Gazzaniga A. Enteric coated timed release systems for colonic targeting. Int J Pharm. 1994;111:99-102.

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

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

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

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

22. Bussemer T, Bodmeier R. Pulsatile drug release from coated capsules. AAPS Pharm Sci. 1999;1(4 suppl):434 (1999).

23. Amidon GL, Leesman GD. Pulsatile Drug Delivery System. US Patent No. 5,229,131; 1993.

24. Ueda S, Ibuki R, Kimura S, Murata S, Takahashi T, Tokunaga Y, Hata T. Development of a novel drug release system, time controlled explosion system (TES). Part III: relation between lag time and membrane thickness. Chem Pharm Bull. 1994;42(2):364-367.

25. Hata T, Shimazaki Y, Kagayama A, Tamura S, Ueda S. Development of a novel drug delivery system (TES): Part V: animal pharmacodynamic study and human bioavailability study. Int J Pharm. 1994;110:1-7.

26. Chen C-M. Multiparticulate Pulsatile Drug Delivery System. US Patent No. 5,508,040; 1996.

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

28. Guo X. Physicochemical and Mechanical Properties Influencing the Drug Release From Coated Dosage Forms. Doctoral Thesis. The University of Texas at Austin;1996.

29. Narisawa S, Nagata M, Hirakawa Y, Kobayashi M, Yoshino H. An organic acid-induced sigmoidal release system for oral controlled-release preparations. Part II: permeability enhancement of Eudragit RS coating led by the physicochemical interactions with organic acid. J Pharm Sci. 1996;85(2):184-188.

30. Richards Grayson, A. C. *et al*. *Nature Mater*. **2,** 767–772 (2003).

31. Dashevsky A and Mohamad A (2006) Int. J. pharm.318:124-131.