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Chronotherapy: A Novel Concept In Drug Delivery

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Abstract

Recent advances in chronopharmacology and requirement of an appropriate technology to deliver the drug at specific time and site led to the development of novel type of drug delivery systems as "chronotropic drug delivery systems". Rationale behind designing these drug delivery systems is to release the drug at desired time (pathophysiological need of disease), which results into improved therapeutic efficacy and patient-compliance. These systems are meant for treatment of those diseases that are caused due to circadian changes in body and when zero order drug release is not desired. These drug delivery systems are designed to release the drug within a short period of time, immediately after a predetermined lag time. Chronotropic systems are promising drug delivery systems in asthma, peptic-ulcer ,cardiovascular diseases, arthritis, attention-deficit syndrome in children and hypercholestremia e.t.c. Approaches like capsular systems, systems with different type of barrier coatings, stimuli sensitive pulsatile systems and externally regulated systems are summarized in this article. This article mainly focuses on diseases requiring chronotropic systems, approaches to design them, recent technologies for chronotherapy and currently available marketed formulations.

Keywords: circadian rhythm, pulsatile drug delivery system, chronotherapy, erodible systems, rupturable systems

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INTRODUCTION

The leaves of certain trees open during day and close at night, showing a clear rhythmicity [**1]**.Circadian rhythms of behavior in mammals are known to be robust and precise. The efficacy and toxicity of many drugs depends upon the relationship between the dosing schedule and the 24 hour rhythms of biochemical, physiological and behavioral processes. Also several drugs cause alterations to 24 hours rhythms leading to illness and altered homeostatic regulation. Alteration in biological rhythm is also a novel concept of adverse effects, which can be minimized by optimizing the dosing schedule [**2].**

Traditionally, drug delivery was only concerned with drug absorption which should be predictable from gut or site of injection. Besides this, second generation drug delivery was meant to achieve perfection in continuous and constant rate delivery of bioactive agents. Since living organisms do not show "zero order" requirement or response to drugs and they are predictable resonating dynamic systems, so they require different amounts of drug at predictably different time within circadian cycle which will maximize desired and minimize undesired drug effects.

Hence rationale behind developing chronotropic systems is **(a)** treatment of diseases in which circadian rhythms play important role in their pathophysiology (chronopharmacotherapy)**(b)** minimize the degradation of drugs in upper gastrointestinal tract (proteins and peptides) **(c)** for programmed delivery of hormones(since continuous release dosage forms may lead to disturbance in normal feed back mechanism of body as well as development of resistance may also take place) and **(d)** for delivery of those drugs which develop biological tolerance (e.g. nitroglycerines) or undergo extensive first pass metabolism and also that are targeted to specific site of gastrointestinal tract e.g. colon[**3]**.

Chronotropic systems are based on the concept of chronopharmaceutics in which there is a transient release of certain amount of drug within a short period of time immediately after a predetermined off-release period.

1.1 Concept of chronotherapy and chronopharmaceutics:

Chronopharmaceutics includes pharmaceutical application of "Chronobiology" in drug delivery. Chronobiology is the study of biological rhythms and their responses to other metabolic functions of body. There are three types of mechanical rhythms in our body: (a***)Circadian rhythms***:-The term "circadian" was obtained from Latin words "circa" meaning "about" and "dies" meaning "day". Oscillations in our body that are completed within 24 hours are termed as circadian rhythms. (b)***Ultradian rhythms***: - Oscillations that are completed in a shorter duration of less than 24 hours are termed as ultradian rhythms (more than one cycle per day).(c)***Infradian rhythms***: - Oscillations that are completed in more than 24 hours are termed as infradian rhythms(less than one cycle per day)

For development of a chronotropic or pulsatile drug delivery system, thorough knowledge of pathogenesis of disease and role of circadian rhythm in its pathophysiology is required. Hence these systems are generally designed for the diseases having enough scientific background to justify their need for chronotropic systems as compared to conventional drug delivery systems.

Diseases such as bronchial asthma, myocardial infraction, angina pectoris, rheumatic disease, ulcer, diabetes, attention deficit syndrome, hypercholestremia and hypertension show symptomatic changes due to circadian rhythmicity.

Aggravations of asthmatic attacks occur in early morning or after midnight due to low lung function promoted by circadian changes at that time. Also cardiovascular diseases like angina, hypertension, myocardial infraction and stroke e.t.c are more prone in early morning. Circadian changes also contribute in lipid metabolism in patients as well as in normal subjects, leading to complication in cholesterol synthesis in patients[**4].** Role of circadian changes in glucose level and insulin synthesis has been extensively studied. Peptic ulcer also favors the noctuctunal acid breakthrough due to circadian variation. In case of rheumatoid arthritis, level of C - reactive protein increases early morning leading to enhanced pain and inflammation**.**

2. Designing of chronotropic systems

Numerous methodologies have been developed to design chronotropic systems to achieve desired drug-release profile in a pulsatile fashion.

2.1 Timed-release/time-dependent chronotropic systems.
2.2. Stimuli dependent systems (pulsatile drug delivery systems).

2.1 Timed-release/time- dependent chronotropic systems

These types of systems show a burst release of drug immediately after a predetermined lag time. Depending on methodologies applied to design them, these systems can be further classified into following subtypes:

Reservoir systems with rupturable polymer coating:

These systems may be either single unit or multiparticulate reservoir systems with outer rupturable barrier. Upon entry of water within the systems, a hydrostatic pressure develops which leads to rupturing of surrounding polymeric layer resulting drug release from the core of system. Pressure buildup required to rupture the coating can be achieved by using swelling agents, gas producing effervescent agents or osmogens. Rate of water permeation and mechanical resistance of the outer membrane are major factors affecting the lag time. Drug release mechanism is based on either diffusion or dissolution according to the nature of drug. Ueda et al. discovered time controlled explosion systems for water insoluble drugs in both single as well as multiple unit dosage forms [**5-8].** Both types of dosage forms contain a core of drug plus osmotic agent and super disintegrants. Finally the cores are coated with a protective polymeric rupturable layer and a top water insoluble semipermeable layer, which is the rate controlling membrane for influx of water into osmotic core. Different type of release pattern can be obtained in different types of dosage forms, for instance in case of tablets, drug is released quickly after the explosion of outer membrane while in case of pellets or granules, drug is released with zero order pattern after a definite lag time because of the time variance of the explosion of the outer membrane. In each bead or granule, drug release is time controlled by the rupturing of external water insoluble membrane caused by explosive swelling effect of the swelling agents. The lag time increases with increasing coating level and higher amount of talc and plasticizer in coating .Drug release from time controlled explosion systems was found to be complete, independent of environmental pH and drug solubility. But there is a drawback of

failing to release drug if swelling agents fail to rupture the water insoluble coating and having limited flexibility in the release pattern.

In order to attain a better control over release pattern ,water soluble polymer(mainly pH dependent) can be incorporated in insoluble polymeric membrane so that at elevated pH of small intestine, polymer starts dissolving leading to weakening of membrane after a predetermined lag time. By variation in coat thickness as well as proportion of soluble and insoluble material in the coating, the lag time before drug release can be prolonged with better control and reliability and eventual disintegration of coating ensuring release of drug[**9]**.Diclofenac sodium pulsatile release pellets were prepared by extrusion-spheronisation technology and coated in a mini fluidized bed spray coater with swelling material as the inner coating swelling layer and ethyl cellulose aqueous dispersion as the outer coating controlled layer. The lag time for pulsed delivery of diclofenac was found to be good agreement between in vitro and in vivo.

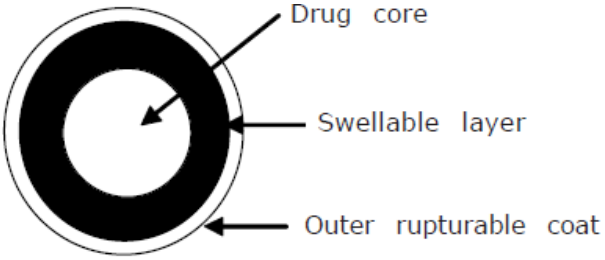

Fig1. Schematic diagram of reservoir systems with rupturable coating layer

Capsular systems

Capsular systems are mainly consisted of an insoluble capsule body and swellable and degradable plugs made of approved substances. The lag time is controlled by plug, which is pushed away by swelling or erosion and drug is released as a pulse from the insoluble capsule i.e. “Pulsincap” . A swellable hydrogel seals the drug contents into the capsule body. Upon coming in contact of dissolution medium, the hydrogel plug swells and after a lag time, the plug pushes itself outside the capsule and rapidly releases the drug. Hydrophilic polymers are generally used for plugs like hydroxypropylcellulose, polyvinyl-acetate, and polyethylene-oxide e.t.c. The swelling strength of plug decides the lag time. Many of the drugs have been formulated in form of pulsincap systems for hypertension, angina, peptic ulcer etc. Gohel and Sumitra developed a system wherein weighed quantity of dicalcium phosphate was filled into the capsule body followed by drug (Diltiazem HCl). Weighed amount of the hydrophilic swellable polymers such as HPMC or guar gum was placed on top and compressed lightly using a rod to form a compact plug [**10]**. To simplify this technology the hydrogel plug has been replaced by an erodible tablet, which has a tight fit in the capsule. To prevent the entry of fluid during the release process it erodes away from the mouth of capsule [**11]**.

Chronotropic systems dependent on changed membrane permeability*:*

Drug release in such type of systems is achieved by change in permeability of polymeric coating layer in presence of certain counter ions of surrounding media. Narisawa et al developed a device capable of pulsed-release depending on the change in diffusion properties of Eudragit RS **[12-13]**. They studied and justified that cores of theophylline coated with Eudragit RS show very

slow release in pure water but release rate increases significantly when the microcapsules are immersed in an organic acid solution containing succinic acid, glutaric acid, tartaric acid, malic acid or citric acid. The above phenomena occurs due to higher hydration of film containing quaternary ammonium groups in the polymer chain and that is not affected by succinic acid, suggesting that the quaternary ammonium groups of Eudragit RS are essential to produce unique drug release profile. The release profile of systems based on permeability changes depend strongly on physicochemical properties of the drug and its interaction with membrane. Therefore, with this system a pulsatile release profile may be obtained for some particular drug molecules in a specific formulation but can not be generally applied to all drugs.

Reservoir systems with soluble/eroding polymer coating:

This class of reservoir type pulsatile systems posses a barrier layer, which dissolves or erodes after a specific lag time followed by burst release of drug from the reservoir core. In these types of systems, the lag time prior to drug release is controlled by thickness of coating layer. A chronotropic system which consists of a drug containing core layered with HPMC and a top layer of enteric coating, the lag time before drug release will be dependent upon the thickness and viscosity grade of HPMC layer. Since drug release mechanism in these types of systems is dissolution, that's why, a high degree of drug solubility relative to dose of drug is essential for rapid release of drug after the lag period. Various grades of hydroxyl propyl methyl cellulose and Eudragit (acrylate) polymers have been studied to in an attempt to deliver drugs to various sites in gastrointestinal tract due to their solubility and eroding properties. Formulations dependent on slow dissolution behavior of high viscosity polymers was described by Gazzaniga et al. by formulation of mini tablets of drug substance which is coated with a high viscosity polymer (HPMC 40000) and an outer enteric coating .The outer film protects the system from fluids in the stomach and dissolves upon entering in small intestine. HPMC layer delays the drug release for 3-4 hours when the system is transported through small intestine [**14].**

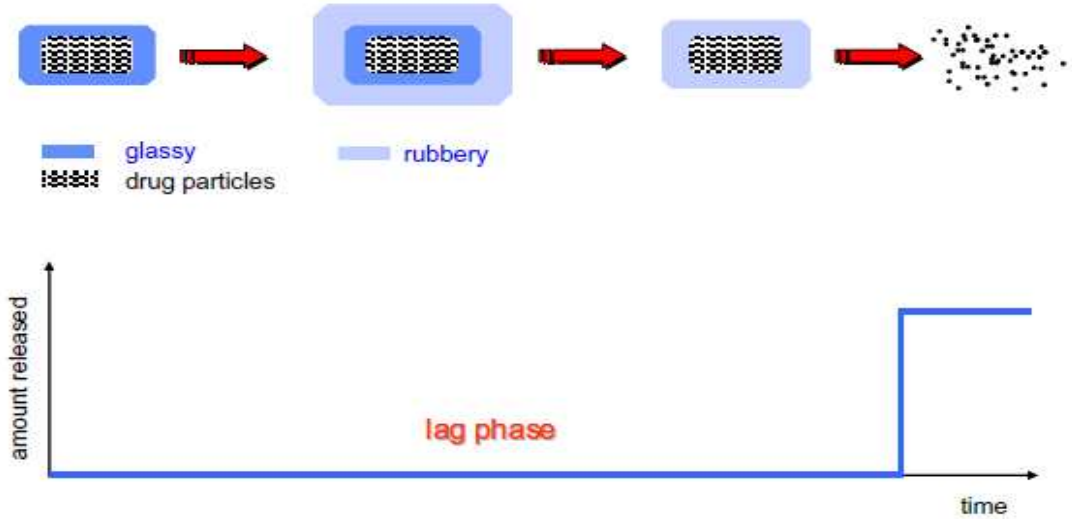

Fig.2 Expected behavior and release profile of swellable/erodible reservoir systems for oral pulsatile delivery

Low density/floating systems:
Nowadays floating dosage forms are gaining importance as technological drug delivery systems with gastro-retentive behavior, offering several advantages in drug delivery. Like treatment of gastrointestinal disorders such as gastro-esophageal reflux, improved drug absorption (because of increased GRT) , ease of administration and better patient compliance [**15**]. These systems are comprised of low density/floating pulsatile dosage forms which are retained in stomach for long time (4-12 hours) and not affected by variation in gastric pH, local environment or gastric emptying rate. These dosage forms may be either single unit (floating tablets) or multiparticulates (beads, pellets, granules, microspheres) with capability of gastro-retention. These systems are specifically beneficial for drugs ,either absorbed from the stomach or requiring local delivery in stomach. Generally polysaccharides are widely accepted in gastroretentive delivery systems because of their simplicity to formulate the drug delivery system and achieve the desired drug release profile. Badave *et. al* developed hollow calcium pectinate beads for floating pulsatile release of diclofenac sodium intended for chronotherapy **[16].**

A multiparticulate floating pulsatile drug delivery system was developed using porous calcium silicate (Fluorite RE) and sodium alginate for time and site specific drug release of meloxicam for chronopharmacotherapy of rheumatoid arthritis **[17].** Meloxicam was adsorbed on the Fluorite RE by fast evaporation of solvent from drug solution containing dispersed Fluorite. Drug adsorbed fluorite powder was used to prepare calcium alginate beads by ionotropic gelation method. The floating time for this system was controlled by density of beads and hydrophobic character of drug. To overcome limitations of various approaches for imparting buoyancy hollow/porous calcium pectinate beads were prepared by simple process of acid base reaction during ionotropic cross linking. The floating beads provide two- phase release pattern with initial lag time during floating in acidic medium followed by rapid pulse release in phosphate buffer. These drug delivery systems show distinct behavior from other approaches in chronotherapy with desired low drug release in acidic medium, reduced time consumption due to single step process and also overcame the limitations of process variable caused by multiple formulation steps.

2.2 Stimuli dependent systems (pulsatile drug delivery systems):
Such systems are novel drug delivery approaches meant for targeted drug delivery at specific site due to induction of certain physiochemical stimuli at target site. Release of certain enzymes, hormones, antibodies, pH of the site, temperature of the site, presence of certain cells, and concentration of biomolecules (glucose, neurotransmitters, inflammatory mediators) act as stimuli to trigger the release of drug from these types of drug delivery systems.

***Temperature sensitive pulsed- release delivery systems*:**
Physiological temperature of various types of cells inside the body is not same due to their different metabolic functions. Certain cells posses some what different temperature (either higher or lower) with respect to other cells like tumor cells, in which cellular temperature is raised due to their higher metabolic rate. For targeting tumors, a pulsatile drug delivery system can be designed by utilizing thermo-responsive hydrogel system. As the name suggests, these polymers undergo swelling/deswelling phenomena in response to temperature change (at different metabolic rates of tumors cells) which modulates drug release from these systems. Y.H Bae. *et al*

developed indomethacin pulsatile drug delivery system in temperature range of 20^0C -30^0C by using reversible swelling properties of copolymers of N-isopropyl acrylamide and butyrylacrylamide. Kataoka.*et.al* developed the thermo-sensitive polymeric micelles as drug carrier to treat cancer.

Inflammation induced systems:

Any physical or chemical stress (injury, fracture e.t.c), which may lead to inflammation, acts as a stimulus (due to hydroxyl radicals produced from inflammation responsive cells).In favor of this Yui and coworkers *et.al* designed and developed inflammation responsive pulsatile drug delivery system which responded to hydroxyl radicals and degraded in a limited manner. They utilized hyaluronic acid which is specifically hydrolyzed by hyaluronidase or free radicals present at inflammatory site abundantly rather than normal tissue. Hence it became possible to treat patient with inflammatory diseases like rheumatoid arthritis, using NSAIDS incorporated into hyaluronic acid gels as a new implantable drug delivery system.

Enzyme dependent pulsatile-release systems:

Such systems are generally developed for colonic delivery of drug since release rate of drug is dependent upon the catalysis of polymeric membrane by enzymes secreted by colonic microflora. Therefore these systems are more specific for targeting, independent of pH variations along the gastrointestinal tract. Numerous natural polysaccharides such as chondroitin sulphate, pectin, dextran, guar gum e.t.c have been investigated for their potential in designing colon specific drug delivery. The use of polysaccharides for coating purposes has been tried with limited success. Most of the non starch polysaccharides suffer from the drawback of lacking good film forming properties. Also they tend to swell in gastrointestinal tract and become porous resulting in early release of drug. Chronotherapy of rheumatoid arthritis has been tried by utilizing these polymers to deliver NSAIDS in colon after a lag time of 4-6hours to relieve pain in early morning. Also pulsatile delivery of 5-aminosalicylic acid has been attempted in case of irritable bowl syndrome.

***Glucose concentration dependent insulin release systems*:**

It was depicted earlierly that there is an increase in blood glucose concentration rhythmically in Diabetes-mellitus Type1. Several systems were developed which responded to changes in glucose concentration. One such stimuli induced system includes pH sensitive hydrogel containing glucose-oxidase enzyme immobilized in hydrogel. As the blood concentration of glucose rises, glucose-oxidase converts glucose into gluconic acid, which changes the pH of system. Due to change in pH, swelling of polymer takes place and this result into insulin release. Insulin decreases the blood glucose level and consequently the gluconic acid level also declines and system turns to deswelling and hence decreasing the insulin release. Examples of pH sensitive polymers include n, n-dimethyl amino ethyl methacrylate, chitosan, polyol e.t.c.

Okan *et.al* developed the system based on the fact that boronic acid moiety forms reversible bonds with polyol compounds including glucose. They used water soluble copolymers containing phenyl boronic acid side chains which showed formation of a reversible complex gels with polyol compounds such as PVA. Such complexes are dissociated after the addition of glucose in a concentration dependent manner.

Intelligent gels responding to antibody concentration

Resistance as well as tolerance towards antibiotic concentration is a common phenomenon shown by microbes in many of the infectious diseases. Hence in order to kill all microbes, both multiplying as well as in dormant phase, a pulsatile release of antibiotic is desired. Novel kind of gels have been developed the respond to change in antibiotic concentration to alter their swelling/deswelling characteristics. Utilizing the difference in association constants between polymerized antibody and naturally derived antibody towards specific antigens reversible gel swelling/deswelling and drug permeation changes occur.

***pH sensitive pulsatile drug delivery systems* :**

pH dependent polymers are widely accepted and most versatile approach to achieve a desired lag time before drug release in a chronotropic system. Either single unit or multiparticulate dosage forms, they show reliable and predictable drug release profile. These systems take the advantage of fact that there exists different pH environment at different parts of gastrointestinal tract. Hence utilizing pH dependent polymers, targeting at specific site of gastrointestinal tract is possible as well as a desired lag time can be achieved due to dependency of polymer solubility only at a particular pH of gastrointestinal tract. Generally pH dependent polymers include copolymers of methacrylic acid (various grades of Eudragit), phthalates, carboxymethylcellulose e.t.c .these polymers are utilized for enteric coating to protect the drug from degradation in upper G.I.T and attain drug release at specific part of intestine (according to solubility of polymer at particular pH and specific site of intestine) after a predetermined lag time. A number of chronotropic systems have been developed and marketed for chronotherapy utilizing pH dependent polymers for asthma, angina, rheumatoid arthritis, cancer, diabetes and ulcer e.t.c. Akhgari *et.al* studied on the optimum ratio of eudragitl100 and Eudragit S1000 for colonic delivery of indomethacin pellets for chronotherapy of rheumatoid arthritis **[18]**. In a study Gupta *et.al* attempted to exploit various grades of Eudragit soluble at pH more than 7 to achieve colonic delivery of 5-aminosalisylic acid for treatment of irritable bowl syndrome **[19]**. Also colon targeted chronotropic systems of theophylline, diltiazem, verapamil; budesonide, nitroglycerine etc have been formulated to treat asthma, angina and hypertension.

3. Dosage Form Development

Multi-Layered tablets or capsules

Such systems are generally time controlled rupturable pulsatile drug delivery systems either in form of hard gelatin capsules or tablets. In case of capsules, drug filled in capsule-body is either for single pulse or multi-pulse release (in form of multiparticulates) which is coated over with a swelling layer followed by an external water insoluble semipermeable polymeric coating. Upon water ingress the swelling layer swells to attain a threshold hydrodynamic pressure required to rupture the outer coating and allowing the release of contents in surrounding medium. The time required by swelling layer to rupture outer coating serves the purpose of desired lag time required in chronotherapy of disease [**20].**The tablets are manufactured and coated on the same principle as that of double coated gelatin capsules.

Press coated tablets

These are timed release formulations, simple to manufacture, comprised of an inner core that contains an active pharmaceutical ingredient and excipients surrounded by an outer layer that

dissolves or disintegrates slowly to produce the lag time. The core is placed between two layers of polymer and directly compressed by flat punches of tabletting machine. Surrounding polymeric layers protect the drug from release before the desired lag time, hence effective delivery in chronotherapy as it allows the drug release at the point in circadian cycle when clinical signs develop and increase. Drugs that treat cardiovascular disease (nifedipine, nitrendipine, amlodipine, diltiazem e.t.c) and asthma (theophylline, budesonide) had been attempted to formulate such dosage forms. Sawada *et al*. prepared timed release compression coated tablets of nifedipine for chronotherapy of angina and compared its invitro-invivo release profile with sustained release formulation **[21]**.

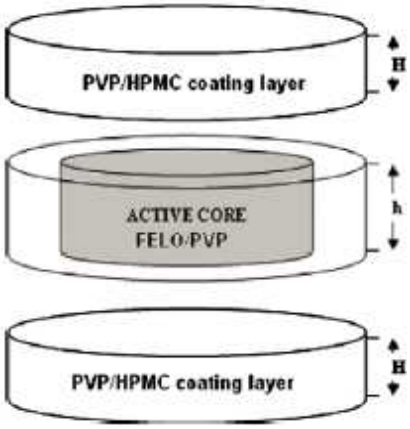

Fig.3 Design of the press-coated system composed of FELO/PVP 10/90 w/w (black color) and an inactive and adjusting coating layer containing different PVP/HPMC ratios (h = expected rupture area)

Core-cup-tablets

The system consists of three different components, a core tablet containing the active ingredient, an impermeable outer shell and a top cover layer-barrier that should be removed at predetermined time. Ideally, the drug should be released after a complete removal of the top cover layer, with the lag time being controlled by the characteristic properties of the material in the top cover. The impermeable coating cup consisted of cellulose acetate propionate and the top cover layer of hydrophilic swellable materials such as polyethylene oxide, sodium alginate or sodium carboxymethylcellulose. The system releases the drug after a certain lag time generally due to the erosion of top cover layer. The quantity of material, its characteristics (viscosity, swelling, gel layer thickness) and the drug solubility was found to modify lag time and drug release. The lag time increases when quantity of top layer increases, whereas drug release decreases.

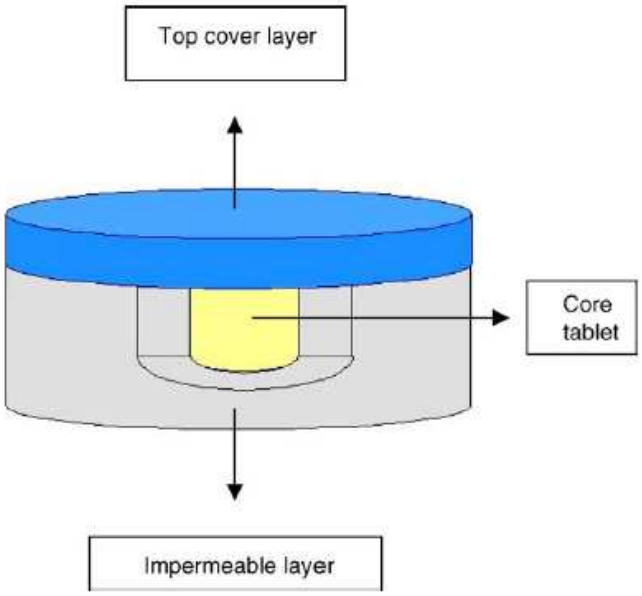

Fig.4 Schematic representation of "core in cup tablet" as a pulsatile drug delivery system

Multiparticulate systems

Such systems have been designed on the basis of various methodologies of designing pulsatile drug delivery system discussed earlier (like time controlled, stimuli induced or externally regulated pulsatile drug delivery systems). Various types of multiparticulate dosage forms are: Pellets, microsponges, microspheres, granules, nanoparticles and Beads e.t.c. Multiparticulate dosage forms are gaining much more importance over single unit dosage forms due to their potential advantages over single unit dosage forms. The potential benefits include increased bioavailability, predictable, reproducible, and generally short gastric residence time; no risk of dose dumping; reduced risk of local irritation; and flexibility to blend pellets with different compositions or release patterns. Because of their smaller particle size, these systems are capable of passing through gastrointestinal tract easily, leading to less inter- and intra-subject variability. A no. of multiparticulate pulsatile drug delivery systems have been developed for chronotherapy. For instance, colonic delivery of theophylline in form of microspheres and coated pellets for nocturnal asthma [**22]**, formulation of pellets and microspheres of NSAIDS (indomethacin, ibuprofen, flurbiprofen, meloxicam, aceclofenac, diclophenac) for chronotherapy of rheumatoid arthritis and floating beads of alginates encapsulating the active drug component in core, have been attempted to deliver many of the drugs which are absorbed in upper gastrointestinal tract. Numerous advanced technologies have been developed in designing of pulsatile release multiparticulate dosage forms and many of them are FDA approved and being marketed.

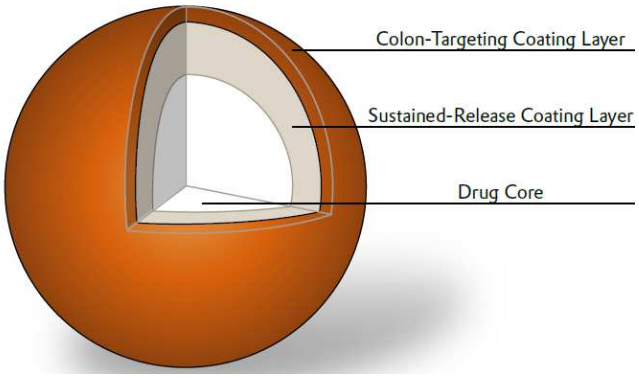

Fig.5 Hypothetical design of a pellet with multiple coating

Pulsincap systems:

These are the well designed pulsatile release drug delivery systems capable of releasing drug at a pre determined time. Drug formulation is contained within the insoluble capsule body which is sealed by means of a hydrogel plug. On oral administration the water soluble capsule cap dissolves in the gastric juices and hydrogel plug swells. At a controlled and predetermined time point after the ingestion, the swollen plug is ejected from the pulsincap dosage form after which the encapsulated dosage formulation is then released **[23]**. To simplify this technology, the hydrogel plug has been replaced by an erodible tablet, which has a tight fit in capsule to prevent the entry of fluid. During the release process it erodes away from the mouth of capsule [**24].** The effect of various parameters such as type and weight of swellable polymer, type of hydrophilic polymers used in erodible tablet formulation and erodible tablet weight was investigated in order to characterize the lag time and drug release profiles.

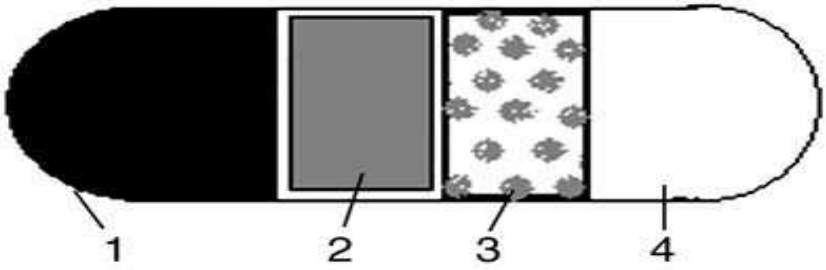

Fig.6 Capsule assembly containing (a) swelling polymer, (2) core tablet, (3) erodible tablet (4) Soluble cap

Infusion pumps

These are externally and internally controlled, pre-programmed systems and sensitive to modulated enzymatic or hydrolytic degradation, pH, magnetic fields, ultrasound, electric fields, temperature, light and mechanical stimulation. Infusion pumps recently in the market that have been referred as "chronomodulating infusion pumps" for drug delivery application include the ***"Melodie", "Programmable-Synchromed", "Panomat V5 infusion"***, and the ***"Rhythmic Pumps"***. The portable pumps are usually characterized by a light weigh (300–500 g) for easy

portability and precision in drug delivery. In case of insulin therapy, implantable infusion pumps containing a reservoir of insulin may be surgically placed within the subcutaneous tissue of the abdomen in the left upper or lower quadrant (above or below the belt). A catheter leads from the pump through the muscle layers into the peritoneal cavity, where it floats freely, and insulin delivery is by the intraperitoneal route. The insulin reservoir is refilled once a month or every 3 months at a physician's office by inserting a needle through the skin into the pump (a local anesthetic is first used). Doses adjustments are made by the patient (within ranges established by the physician) using radiotelemetry and an electronic device that is held over the pump. Their advantages include the fact that the peritoneum provides a large, well-vascularized surface area, and absorption is faster by this route than after subcutaneous injection (better insulin gradient), improved glycemic control and a reduction in the frequency of hypoglycemic episodes. Possible drawbacks of this approach include eventual formation of fibrous tissue pocket and local skin erosion. Cathether blockade which can reduce insulin delivery, are the most common problems with implantable pumps. However, these pumps have been effectively used in the chronotherapy of several diseases such as cancer and diabetes.

Chronomodulating-microchips

Micro-fabrication technology is an alternative method to achieve pulsatile or chronopharmaceutical drug release. Santini *et. al*. reported a solid-state silicon microchip that can provide controlled release of single or multiple chemical substances on demand [**25]**. The release mechanism was based on the electrochemical dissolution of thin anode membranes covering microreservoirs filled with chemicals in solid, liquid or gel form. This technology has the potential to be used in the design of chronotropic drug delivery systems with a better control over drug release kinetic in order to match biological requirement over a versatile period of time.

4. Advances in pulsatile drug delivery

Chronotropic systems are one of the interesting novel drug delivery systems emerging for chronotherapy due to advanced technologies and desired therapeutic application. Among these, multiparticulate systems (beads, pellets, microspheres e.t.c) are gaining more importance than single unit systems due to their potential benefits over them. Various pulsatile technologies have been developed on the basis of approaches discussed previously. These include:

CODOS

Term CODOS stands for "Chronotherapeutic Oral Drug Absorption System", which is a multiparticulate system designed for bedtime drug dosing, incorporating a 4–5 hr delay in drug delivery. This delay is introduced by the level of non-enteric release-controlling polymer applied to drug loaded beads. The release controlling polymer is a combination of water soluble and water insoluble polymers. As water from the gastrointestinal tract comes into contact with the polymer coated beads, the water soluble polymer slowly dissolves and the drug diffuses through the resulting pores in the coating. The water insoluble polymer continues to act as a barrier, maintaining the controlled release of drug. The rate of release is essentially independent of pH, posture and food. The nighttime dosing regimen of (CODAS-Verapamil) was not associated with excessive BP reductions during the sleeping hours. The CODAS-verapamil extended release capsules (Verelan PM) as chronotropic dug delivery systems actually provided enhanced BP

reduction during the morning period when compared with other time intervals of the 24-h dosing period.

OROS

OROS technology is based on osmotic mechanism to provide pre-programmed, controlled drug delivery to the gastrointestinal tract. Osmotic systems utilize the principle of osmotic pressure for the delivery of drugs. Drug release from these systems is independent of pH and other physiological parameter to a large extent and it is possible to modulate the release characteristic by optimizing the properties of drug and system [**26].**The dosage form comprises a wall that defines a compartment. The active drug is housed in a reservoir, surrounded by a semi-permeable membrane/wall (e.g. cellulose esters, cellulose ethers and cellulose ester–ethers) and formulated into a tablet. The tablet is divided into two layers, an active drug layer and a layer of osmotically active agents (e.g. poly ethylene oxide). Water from the gastrointestinal tract diffuses through the membrane at a controlled rate into the tablet core, causing the drug to be released in solution or suspension at a predetermined rate. This creates a 'pump' effect that pushes the active drug through a hole in the tablet. This technology, especially the **OROS**, Delayed Push– Pull System, also known as controlled onset extended release **(COER)** was used to design **Covera**, a novel anti-hypertensive product. It actually enabled delayed, overnight release of verapamil to prevent the potentially dangerous surge in BP that can occur in the early morning [**27]**.

$TIMER_X$

The TIMERx technology (hydrophilic system) has been developed by utilizing time dependent natural polymers obtained primarily from xanthan and locust bean gums mixed with dextrose. Physical interaction between these components leads to the formation of strong binding gel in the presence of water. Drug release is controlled by the rate of water penetration from the gastrointestinal tract into the TIMERx gum matrix, which expands to form a gel and subsequently releases the active drug substance. This system can precisely control the release of the active drug substance in a tablet by varying the proportion of the gums, together with the third component, the tablet coating and the tablet manufacturing process

CONTIN

This technology utilizes the concept of molecular coordination complexes formed between a cellulose polymer and a non-polar solid aliphatic alcohol optionally substituted with an aliphatic group by solvating the polymer with a volatile polar solvent and reacting the solvated cellulose polymer directly with the aliphatic alcohol, preferably as a melt. This complex serves as matrix in controlled release formulations since it has a uniform porosity (semipermeable matrixes). This technology has concretely enabled the development of tablet forms of sustained-release aminophylline, theophylline, morphine, and other drugs. Research suggested that evening administration of Uniphyl (anhydrous theophylline) tablets represented a rational dosing schedule for patients with asthma who often exhibit increased bronchoconstriction in the morning. Patients demonstrated improved pulmonary function in the morning compared with use of twice-daily theophylline when once-daily Uniphyl was administered in the evening. Thus, evening administration of once-daily theophylline may block the morning dip in lung function commonly seen. CONTIN technology provides for closer control over the amount of drug

released to the bloodstream, and benefits patients in terms of reducing the number of doses they need to take every day, providing more effective control of disease particularly at night.

DIFFUCAPS

DIFFUCAPS technology is the most popular and versatile approach for chronotherapy for delivering drugs into the body in a circadian release fashion. It is comprised of multiparticulate one or more populations of drug-containing particles (beads, pellets, granules, etc.). Each bead population exhibits a pre-designed rapid or sustained release profile with or without a predetermined lag time of 3–5 h. The active core of the dosage form may comprise an inert particle or an acidic or alkaline buffer crystal (e.g. cellulose ethers), which is coated with a film-forming formulation and preferably a water-soluble film forming composition (e.g. hydroxylpropylmethylcellulose, polyvinylpyrrolidone) to form a water-soluble/dispersible particle. The active core may be prepared by granulating and milling and/or by extrusion and spheronization of API. Such a chronotropic drug delivery system is designed to provide a plasma concentration–time profile, which varies according to physiological need during the day, i.e. mimicking the circadian rhythm and severity/manifestation of a cardiovascular disease, predicted based on pharmacokinetic and pharmacodynamic considerations and in vitro/in vivo correlations. This technology has been used to formulate the first and recently FDA approved propranolol-containing chronotropic system (***Innopran^{R} XL***) for the management of hypertension.

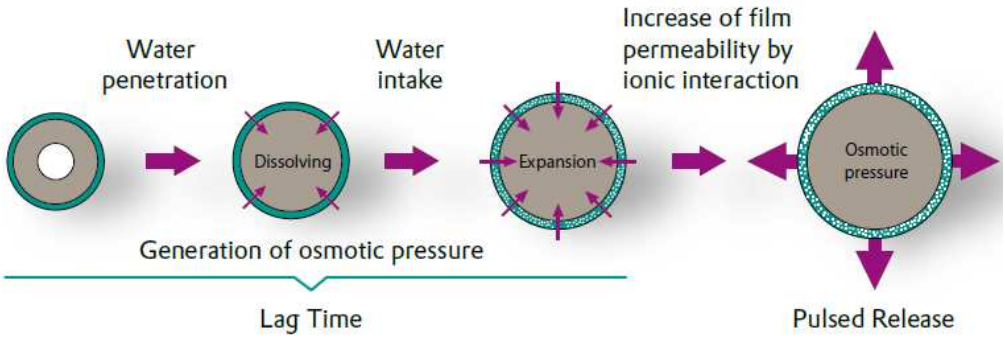

Fig.7 Diagrammatic representation of multiparticulate drug release mechanism in "DIFFUCAPS Technology"

CEFORM

CEFORM technology applies several mechanical forces which allow the production of uniformly sized and shaped microspheres of pharmaceutical compounds. The basic methodology applied in designing of such chronotropic system is based on ''melt-spinning technology'', which involves subjecting of biodegradable polymer/bioactive agents to the combination of temperature, thermal gradients, mechanical forces, flow, and flow rates during processing. The microspheres obtained are almost perfectly spherical, having a diameter that is typically 150–180 µm, and allow for high drug content. The microspheres can be used in a wide variety of dosage forms, including tablets, capsules, suspensions, effervescent tablets, and sachets. The microspheres may be coated for controlled release either with an enteric

coating or combined into a fast/slow release combination. This technology has been actually used to develop "***Cardizem LA***", 1-day Diltiazem formulation as chronotropic systems.

Three Dimensional Printing(Their Form Technology)

It is a fully integrated computer-aided development and manufacturing process. Products may be designed on a computer screen as three-dimensional models before actual implementation of their preparation process. This versatile technology may found potential application in chronopharmaceutics in the future. Three dimensional printing (3DP) is a novel technique used in the fabrication of complex oral dosage delivery pharmaceuticals based on solid free form fabrication methods. It is possible to engineer devices with complicated internal geometries, varying densities, diffusivities, and chemicals. Different Types of complex oral drug delivery devices have been fabricated using the 3DP process: immediate-extended release tablets, pulse release, break away tablets, and dual pulsatory tablets. The enteric dual pulsatory tablets were constructed of one continuous enteric excipient phase into which diclofenac sodium was printed into two separated areas. These samples showed two pulses of release during in vitro with a lag time between pulses of about 4 hr. This technology is the basis of the" Their Form technology". The latter is a micro-fabrication process that works in a manner very similar to an ''ink-jet'' printer.

PULSYS

PULSYS™ technology, pioneered by Middle Brook™ (previously Advancis) Pharmaceuticals, Inc., could be considered a significant step forward in improving current antibiotics treatment regimens. From the very start, the company faced numerous setbacks and challenges before its once-daily amoxicillin (775 mg) product, ***Moxatag***, based on PULSYS™ technology(was approved by the US FDA on 24 January 2008); it was set to enter the market on 16 March 2009 . Moxatag is an extended-release tablet for the treatment of adults and pediatric patients aged ≥ 12 years with pharyngitis and/or tonsillitis secondary to *Streptococcus pyogenes* (commonly referred to as 'strep throat'). The ***PULSYS™*** technology of delivering drug in parallel concomitant pulses corrected the flaws in traditional anti-infective therapy, which relied on single, strong and immediate drug doses that – rather than killing microbes – tend to trigger defensive dormancy in bacteria; studies have shown that antibiotics are most effective against actively growing bacteria. However, traditional anti-infective therapy methods, which focus on immediate-release doses, prompt bacteria to enter a dormant state, in which they may survive the drug. Exposing the bacteria to rapid antibiotic pulses within the first hours of initial dosing was found to have the potential to cripple the natural defense mechanisms of bacteria, eliminating them more efficiently and effectively than conventional anti-infective therapy regimens [**28]**.

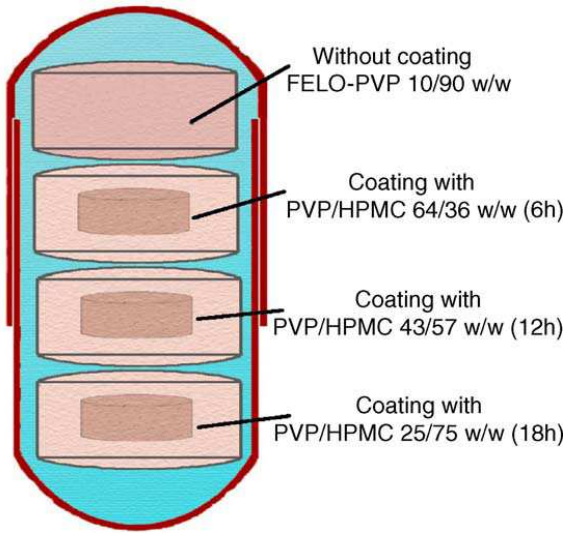

Fig.8 Scalable pulsatile Chronotherapeutic formulations consisted of a capsule containing tablets with different coating layers adjusting precisely the time of FELODIPINE release.

Table no. 1 Marketed technologies of pulsatile drug delivery

Technology	**Mechanism**	**Proprietary name and dosage form**	**API**	**Disease**
OROS®;	Osmotic mechanism	Covera-HS® XL tablet	Verapamil HCl	Hypertension
CODOS®	multiparticulate ph dependent system	Verelan® PM; XL release capsule	Verapamil HCL	Hypertension
DIFFUCAPS®	multiparticulate system	Innopran®;XL tablets	Verapamil HCl, propranolol HCl	Hypertension
Three dimensional printing®	externally regulated system	TheirForm®	Diclophenac sodium	Inflammation
Pulsincap™	Rupturable system	PulsincapTM	Dofetilide	Hypertension

CONCLUSION

Besides lots of experimental and theoretical development, chronotherapy is still in stage of infancy. Market constraints and increasing demand of such drug delivery systems demonstrate the clinical relevance of chronopharmaceutics; hence chronotropic systems are an emerging approach to drug delivery. Chronopharmaceutics assures improved patient outcome and optimized disease management in the future. Dependence of response over human action to trigger the drug release is the major drawback associated with these systems. Hence an ideal chronotropic system should be self regulating, taken any time and should take environmental factors in account (e.g. awake– sleep, light–dark, activity–rest status). For example, the human body is comprised of molecules, hence the availability of molecular nanotechnology that facilitate self-regulation of chronotropic systems based on body immune system and disease state will permit dramatic progress in human medical services. Moreover, the circadian clock of the suprachiasmatic nucleus (SCN) is thought to drive daily rhythms of behavior by secreting factors that act locally within the hypothalamus. The overall success of chronopharmaceutics will depend on the successful integration of knowledge from future advances in development timing, system biology and nanomedicine. The selection of the appropriate chronopharmaceutical technology should take into considerations the application range (e.g. targeted drugs of different physiochemical properties), the ease of manufacturing, the cost-effectiveness, and the flexibility in the pharmacokinetic profile. Pulsatile drug delivery systems are smart and efficient dosage forms satisfying needs of patients and offering interesting options for intelligent life cycle management. In near future due to more advancement of technology, the hurdles in manufacturing and processing steps will be overcome and a number of patients will be greatly benefited by these systems.

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