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A REVIEW ON FORMULATION AND EVALUATION OF PULSATILE DRUG DELIVERY SYSTEM

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ABSTRACT

In the current scenario of pharmaceutical research much attention has been focused on patients' health in terms of therapeutic efficacy and safety thing in mind. Pulsatile drug delivery system is the most interesting time and site specific system. This system is designed for chronopharmacotherapy which is based on cardiac rhythm. pulsatile drugdelivery system is most intresting time and site specific system as per pathophysiologocal need of the disease. Pulsatile drug delivery system is characterized by time of period of no release(lagtime) fallowed by a rapid and complete drug release. The system are beneficial for the drug having chronopharmacological behavior were night time dosing is required and for the drugs having high first pass effect and having specific site of absorption in gastro intestinal tract. The current article focuses on the review of literature concerning the disease requiring PDDS, Methodologies involved in the existing systems, significance of swelling agent, and recent technologies in PDDS.

KEYWORDS: Pulsatile drug delivery, Swelling agent, Swelling Index, Lag time, Chronotherapy, Capsular System.

INTRODUCTION

In the current scenario of pharmaceutical research much attention has been focused on patients' health in terms of therapeutic efficacy and safety so keeping this thing in mind The new devlopment delivery systems works on various principle by providing variable /constant

drug amount over a particular time period and physiological factors however the bodys circidian rhytm and chronotheraphy.[1]

Pulsatile drug delivery system

pulsatile drugdelivery system is most intresting time and site specific system as per pathophysiologocal need of the disease. Pulsatile drug delivery system is characterized by time of period of no release(lagtime) fallowed by a rapid and complete drug release.The drug release was influenced by type of pulsatile delivery system there was employed in formulation(capsular system, osmatic system, rupturable polymeric coating). The lag time was reduced by replacing the swelling agents and disintegrating agents. By reducing the lag time the drug release was done before the actual time of release.[2-1]

Advantages of PDDS

1. Extended day time or night time activity.
2. Reduced side effects.
3. Reduced dose size and dosing frequency.
4. Improved patient compliance.
5. Daily fewer dosage units are required by patients in the therapy and hence daily cost is lowered.
6. Drug adapts to suit circadian rhythms of body functions or diseases.
7. Drug targeting to specific site like colon.
8. Protection of mucosa from irritating drugs.[3-4]

Circadian Rhythm

It is defined as Self-Sustaining, Endogenous oscillations that occur with a periodicity of about 24Hours. Interestingly, the term circadian is derived from the latin circa which means About and Dies Which Can Be defined as—A Day. Normally, circadian Rhythms Are Synchronized According to Internal Biologic Clocks Related to the Sleep-Wake cycle. 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 as shown in fig.1. 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.[6]

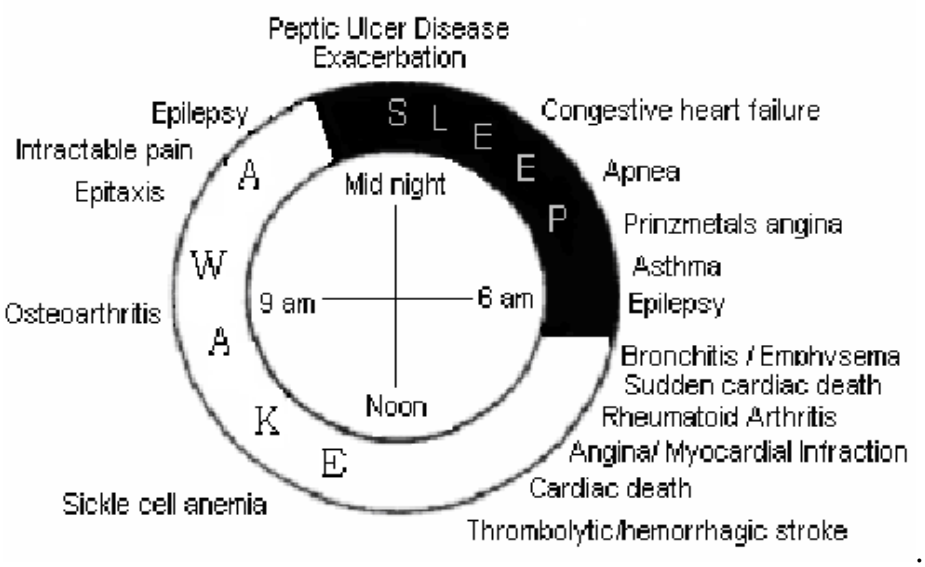

Fig. 1: Cycle of Circadian rhythm.

Table 1: Diseases required pulsatile drug delivery.[7-8]

Disease	Chronological behavior	Drugs used
Peptic ulcer	Acid secretion is high in the afternoon and at night	H2 blocker
Asthma	Precipitation of attacks during the night or early Morning hour	B2 agonist, Antihistamine Leukotrine receptor Antagonist
Cardiovascular disease	BP is at the lowest during sleep cycle and rises steeply during the early morning awakening days.	Nitroglycerin, Calcium channel blocker, and ACE inhibitors
Diabetes mellitus	increase in blood sugar level after meal	Sulfonylurea, Insulin and Biguanides
Hypercholesterolemia	Cholesterol synthesis is generally higher during the night than during daytime	HMG Co A Reductase Inhibitors

CLASSIFICATION OF PULSATILE DRUG DELIVERY SYSTEMS[9]

Pulsatile drug delivery system is classified into fourclasses

A. Time controlled pulsatile release

1. **Singleunitsystem**

i. Capsular system.

ii. Port system.

iii. Delivery by solubility modulation.

iv. Delivery by solubility modulation

v. Delivery by reservoir systems with erodible or soluble barrier coatings.

B. Multi-particulate system

i. Pulsatile system based on rupturable coating.

ii. Time controlled expulsion system.

iii. Pulsatile delivery by change in membrane permeability.

iv. Sigmoidal release system.

v. Low density floating multiparticulate pulsatile systems.

C. Stimuli induced

1. Chemical stimuli induced pulsatile systems
2. External stimuli pulsatile release
3. Micro electro mechanical systems (MEMS)
4. Magnetically induced pulsatile release
5. Pulsatile release systems for vaccine and hormone products

A. Time controlled pulsatile release

I. Single unit systems

1. Capsular System: Different single-unit capsular PDDS have been developed (Fig 2). A general -design of such systems consists of an insoluble capsule body housing a drug and a plug. The plug is removed after a predetermined time lag due to swelling, erosion, or dissolution. The Pulsincap® system is an example of such a system that is made up of a water-insoluble capsule body filled with drug formulation.[10] The body is closed at the open end with a swellable hydrogel plug. Upon contact with dissolution medium or gastro-intestinal fluids, the plug swells, pushing itself out of the capsule after a time lag. This is followed by a spontaneous release of the drug (Fig 2). The time lag can be controlled by manipulating the dimension and the position of the plug. For water insoluble drugs, a spontaneous 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),[11-12] erodible compressed polymers (e.g: hydroxypropylmethyl cellulose, polyvinyl alcohol, I.polyethylene oxide), congealed melted polymers (e.g: saturated polyglycolated glycerides, glycerylmonoole and enzymatically controlled erodible polymer e.g:pectin). These formulations are well tolerated in animals and healthy volunteers, and there have been 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.

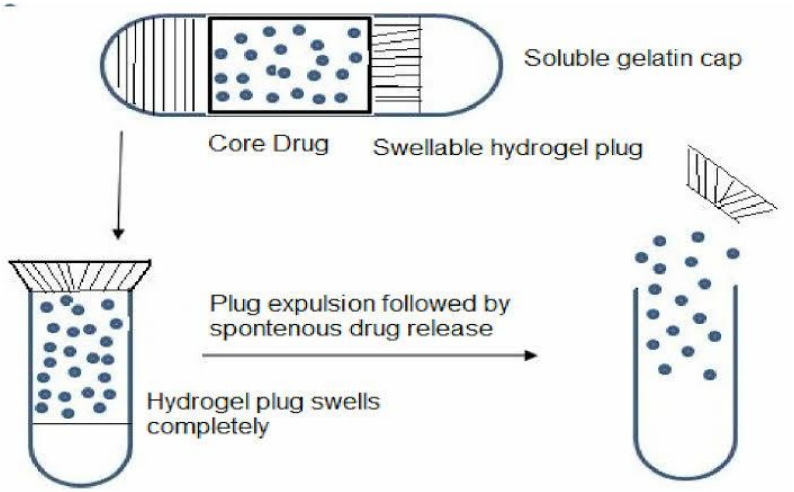

Fig 2: Schematic diagram of capsular system.

2. Port systems: The Port System - consists of a gelatin capsule coated with a semi permeable membrane (e.g: cellulose acetate) housing an insoluble plug (e.g: lipidic) and an osmotically active agent along with the drug formulation.[13] When it comes in pressure that ejects the plug after a – time lag. The time lag is controlled by the thickness of semi permeable membrane. The system showed good correlation in lag times of in-vitro and in-vivo experiments in humans.[14] In order to deliver drug in liquid form, an osmotically driven capsular system was developed. In this system, liquid drug is absorbed into highly porous particles, which release the drug through an orifice of a semi permeable capsule supported by an expandinosmotic layer after the barrier layer is dissolved.[15] The capsular system delivers drug by the capsule's osmotic infusion of moisture from the body. The capsule wall is made up of an elastic material and possesses an orifice. As the osmosis proceeds, the pressure within the capsule rises, causing the wall to stretch. The orifice is small enough so that when the elastic wall relaxes, the flow of the drug through the orifice essentially stops, but when the elastic wall isdistended beyond threshold sufficientlto allow drug release at a required rate. Elastomers, value, the orifice expands such as styrene-butadiene copolymer have been suggested.[16-17]

3. Delivery by a series of stops: 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.[18]

4. Delivery by solubility modulation: These 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.[19] These values show that the solubility of the drug is a function of the modulator concentration, while the modulators solubility is largely independent of drug concentration. The modulating agent can be a solid organic acid, inorganic salt, or organic salt.

5. Delivery by reservoir systems with erodible or soluble barrier coatings: 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 time lag depends on the thickness of the coating layer.[20] The Time Clock system consists of a solid dosage form coated with lipid barriers containing carnauba wax and bees wax along with surfactants, such as polyoxyethylene sorbitan monooleate.[21;22] 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. The major advantage of this system is its ease of manufacture without any need of special equipment. The disadvantage of this system is a premature drug release when the penetrating water dissolves the drug. The Chronotropic system consists of a drugcontaining core coated by hydrophilic swellable hydroxypropylmethyl cellulose (HPMC), which is responsible for a lag phase in the onset of drug release. Time lag is controlled by the thickness and the viscosity grades of HPMC used in coating the drug core. The system is suitable for both tablets and capsule formulations.[23]

II. Multiparticulate Systems: Multi-particulate drug delivery systems are mainly oral dosage forms consisting of a multiplicity of smalldiscrete units, in which the active substance is present as a number of small independent subunits. They provide many advantages over single-unit systems because of their small size, less inter and intra-subject variability in gastrointestinal transit time, reduced adverse effects and improved tolerability, no risk of dose dumping, flexibility in design and finally Improve stability However, there are some draw backs in this system, which include lack of manufacturing reproducibility, high cost of production, multiple formulation steps and also the need of advanceed technologies. There are different types of multiparticulate systems and these are enumerated and explained below.

1. Pulsatile System Based on Rupturable Coating: This is a multiparticulate system in which drug is coated on non-pareil sugar seeds followed by a swellable layer and an insoluble top layer.[24,25] The swelling agents used include superdisintegrants like sodium carboxymethyl cellulose, sodium starch glycollate, L-hydroxypropyl cellulose, etc. 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 a high amount of lipophilic plasticizer in the outer most layer.

2. Time controlled expulsion system: This system is based on a combination of osmotic and swelling effects. The core contains the drug, a low bulk density solid and/or liquid lipid material (e.g., mineral oil) and a disintegrant. The core is further coated with cellulose acetate. Upon immersion in aqueous medium, water penetrates the core displacing the lipid material. After the depletion of lipid material, internal pressure increases until a critical stress is reached, which results in rupture of the coating material.[26] Another system is based on a capsule or tablet composed of a large number of pellets.[27]

3. Pulsatile Delivery by Change in MembranePermeability: 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.[28] 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 it facilitates the interaction of polymer with water,

thereby changing its permeability and allowing to permeate the active core in a controlled manner.

4. Sigmoidal Release System[29]: This consists of pellet cores comprising drug and succinic acid coated with ammonio-methacrylate copolymer USP/NF type B. The time lag is controlled by the rate of water influx through the polymer membrane. The water dissolves acid and the drug in the core. The acid solution in turn increases permeability of the hydrated polymer film. The different types of acids that can be used include succinic acid, acetic acid, glutaric acid, tartaric acid, malic acid, or citric acid.

5. Low density floating multiparticulate pulsatile systems: Conventional multiparticulate pulsatile release dosage forms mentioned above are having longer residence time in the gastrointestinal tract and due to highly variable nature of gastric emptying process may result in in vivo variability and bioavailability problems. In contrary, low density floating multiparticulate pulsatile dosage forms reside only in stomach and not affected by variability of pH, local environment or gastric emptying rate. These dosage forms are also specifically advantageous for drugs either absorbed from the stomach or requiring local delivery in stomach.[30]

B. Stimuli induced pulsatile release system: Several polymeric delivery systems undergo phase transitions and demonstrate marked swellingdeswelling changes in response to environmental changes including solvent composition, ionic strength, temperature, electric fields, and light.[31] Responsive drug release from those systems results from the stimuli-induced changes in the gels or in the micelles, which may deswell, swell, or erode in response to the respective stimuli. The mechanisms of drug release include ejection of the drug from the gel as the fluid phase synerges out, drug diffusion along a concentration gradient, electrophoresis of charged drugs towards an oppositely charged electrode and liberation of the entrapped drug as the gel or micelle complex erodes.[32]

I. Chemical stimuli induced pulsatile systems

1. Glucose-responsive insulin release devices: In case of Diabetes mellitus there is rhythmic increasein the levels of glucose in the body, requiring injection of the insulin at proper time. Several systems have been developed which are able to respond to changes in glucose concentration. One such system includes pH sensitive hydrogel containing glucose oxidase immobilized in the hydrogel. When glucose concentration in the blood increases

glucose oxidase converts glucose into gluconic acid which changes the pH of the system. 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. Examples of the pH sensitive polymers include N, N-dimethylaminoethyl methacrylate, chitosan, polyoletc.[33-34]

2. Inflammation-inducedpulsatilerelease[35]: On receiving any physical or chemical stress, such as injury, fracture etc., inflammation take place at the injured sites. During inflammation, hydroxyl radicals are produced from these inflammation-responsive cells. Degradation via hydroxyl radicals however, is usually dominant and rapid when Hyaluronic Acid gel is injected at inflammatory sites. Thus, it is possible to treat patients with inflammatory diseases like rheumatoid arthritis; using anti-inflammatory drug incorporated with HA gels as new implanted drug delivery systems.

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

4. pH sensitive drug delivery system[36]: This type of PDDS contains two components. Thefirst is fast release type while the other is pulsed release which releases the drug in response change in pH. In case of pH dependent system, advantage has been taken of the fact that there exists different pH environment at different parts of the gastrointestinal tract. By selecting the pH dependent polymers drug release at specific location can be obtained. Examples of pH dependent polymers include cellulose acetate phthalate, polyacrylates, and sodium carboxymethylcellulose. These polymers are used as enteric coating materials so as to provide release of drug in the small intestine.

II. External stimuli pulsatile release: Electrically responsive delivery systems are prepared from polyelectrolytes (polymers which containrelatively high concentration of ionisable

groups along the backbone chain) and are thus, pHresponsive as well as electro-responsive. Examples of naturallyoccurring polymers include hyaluronic acid, chondroitin sulphate, agarose, carbomer, xanthan gum and calcium alginate.[37] The synthetic polymers are generally acrylate and methacrylate derivatives such as partially hydrolyzed polyacrylamide, polydimethylaminopropyl acrylamide.

III. Micro electro mechanical systems (MEMS): A micro fabricated device has the ability to store and release multiple chemical substances on demand by a mechanism devoid of moving its parts.[38-39] The digital capabilities of MEMS may allow greater temporal control over drug release compared to traditional polymer-based systems. Another development in MEMS technology is the microchip. The microchip consists of an array of reservoirs that extend through an electrolyte-impermeable substrate. The prototype microchip is made of silicon and contains a number of drug reservoirs, each reservoir is sealed at one end by a thin gold membrane of material that serves as an anode in an electrochemical reaction and dissolves when an electric potential is applied to it in an electrolyte solution. The reservoirs are filled with any combination of drug or drug mixtures in any form (i.e. solid, liquid or gel). When release is desired, an electric potential is applied between an anode membrane and a cathode, the gold membrane anode dissolves within 10-20 seconds and allows the drug in the reservoir to be released. This electric potential causes oxidation of the anode material to form a soluble complex with the electrolytes which then dissolves allowing release of the drug. Complex release patterns (such as simultaneous constant and pulsatile release) can be achieved from the microchips. Microchip has the ability to control both release time and release rate.

IV. Magnetically induced pulsatile release: The use of an oscillating magnetic field to 1modulate the rates of drug release from polymer matrix was one of the old methodologies. Magnetic carriers receive their magnetic response to a magnetic field from incorporated materials such as Magnetite, Iron, Nickel, Cobalt etc. For biomedical applications, magnetic carriers must be water-based, biocompatible, non-toxic and non-immunogenic mechanistic approach based on magnetic attraction is the slowing down of oral drugs in the gastrointestinal system. This is possible by filling an additional magnetic component into capsules or tablets. The speed of travel through the stomach and intestines can then be slowed down at specific positions by an external magnet, thus changing the timing and/ or extent of drug absorption into stomach or intestines.[40]

V. Pulsatile release systems for vaccine and hormone products: Vaccines are traditionally administered as an initial shot of an antigen followed by repeated booster shots to produce protective immunity. The frequency of the booster shots, and hence the exact immunisation-schedule is antigen dependent. Also, co-administration of vaccine adjuvant is often required to enhance the immune response to achieve protective immunity. PDDS offer the possibility of single-shot vaccines if initial booster release of the antigen can be achieved from one system in which timing of booster release is controlled. Vizcarra et al. found in nutritionally anoestrous cows, GnRH administered in pulses of 2 mg over 5 min every hour for 13 days produced a higher frequency of luteal activity by 13th day than cows given continuous infusions or pulses every 4 hr.

Formulation of Compressed Tablets[41]

The methodology adopted includes

1) **Preparation of core tablets**
2) **Coating of the core tablets**

Formulation of core tablets: The inner core tablets were prepared by using direct compression method as per the developed formulation table which was shown above. Accurately weighed amounts of pure drug, MCC, sodium starch glycolate, Cros carmellose sodium, Cross povidone, and Talc were dry blended for about 15min followed by addition of magnesium stearate. The mixture was then further blended for 10 min. Now the resultant powder blend was manually compressed using punching machine and finally the core tablet was obtained.

Formulation of coated tablets: The optimized core tablets were coated with coating ingredients like Sodium alginate, Ethyl cellulose. Now accurately weighed amount of barrier layer material was transferred into a 16mm die then the core tablet was placed manually at the center. The remaining amount of the barrier layer material was added into the die and compressed. Compression of tablets was done in rotary compression tablet machine using 16.4x8mm flat oval shape punch. The prepared tablet of each batch was evaluated for the tablet properties.

Swelling agent:[42] A swelling agent is a three-dimensional network of hydrophilicpolymer chains that are chemically or physically cross-linked. De-pending on their structure, swelling agents can absorb aqueous or organic solutions. If the former is the case, a swelling agent is

called a hydrogel. Since most swelling agents are hydrophilic in nature, they can absorb significant amounts of gaseous (moisture) or liquid water. The driving force for the absorption or swelling process is generally a balance of three forces of osmotic, electrostatic and entropy-favored dissolution of polymer in waterSwelling agents used in pulsatile dosage form (Sodium alginate, karaya gum). The swelling capacity was calculated by ‘’swelling index.’’

Swelling index: The extent of swelling was measured in terms of % weight gain by the granules. The swelling behavior of all formulation was studied. 2 gm from each formulation was kept in a petridish containing pH 6.8 phosphate buffers. At the end of 1 hour, the petridish along with the granules were weighed. Then weights of the granules, were noted, and the process was continued till the end of 24 hours. The swollen granules were weighed (W2) and the percentage of swelling was calculated by the following equation.

Swelling index = (W2 - W1)/W1*100.

Mechanism of drug release from pulsatile drug delivery system[43]

The mechanism of drug release from PDDS can be occurring in the following ways.

1. **Diffusion:** On contact with aqueous fluids in the gastrointestinal tract (GIT), water diffuses into the interior of the particle. Drug dissolution occurs and the drug solutions diffuse across the release coat to the exterior.
2. **Erosion:** Some coatings can be designed to erode gradually with time, thereby releasing the drug contained within the particle.
3. **Osmosis**: In allowing water to enter under the right circumstances, an osmotic pressure can be built up within the interior of the particle. The drug is forced out of the particle into the exterior through the coating.

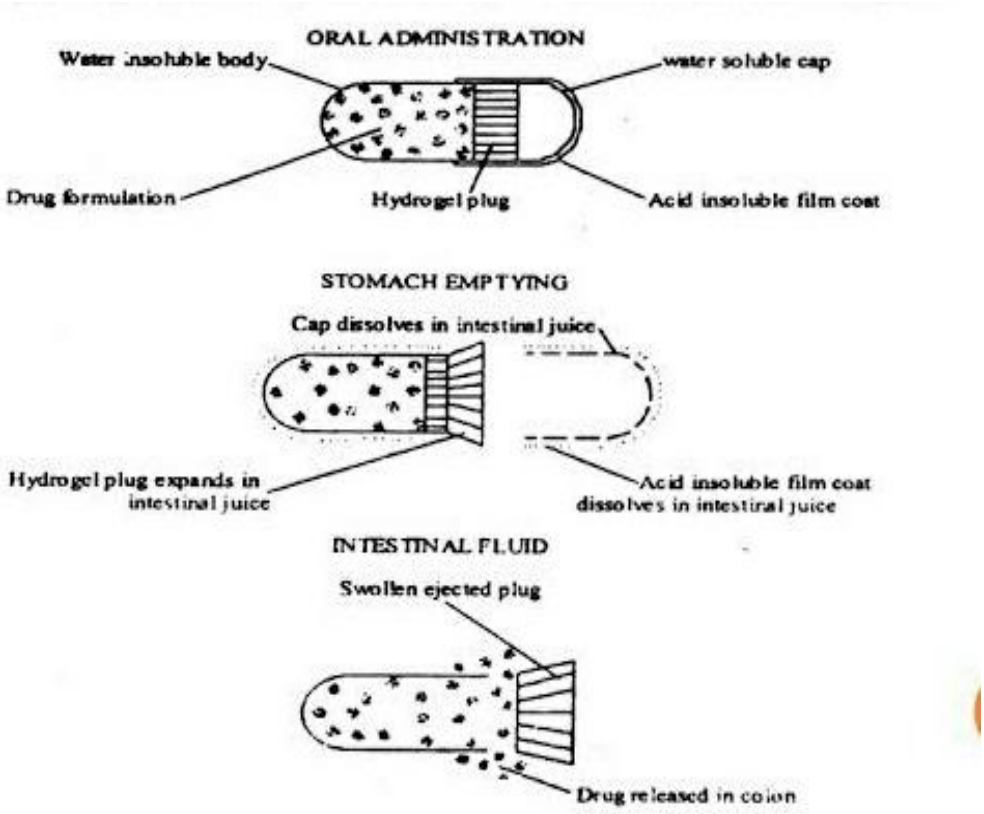

Fig. 3: Release mechanisam of pulsatile drug delivery system.

Evaluation of pulsatile drug delivery system

In vitro and in vivo correlation ((IVIVC)

Correlations between in vitro and in vivo data (IVIVC) are often used during pharmaceutical development in order to reduce development time and optimize the formulation.

1. A good correlation is a tool for predicting in vivo results based on in vitro data. IVIVC allows dosage form optimization with the fewest possible trials in man, fixes dissolution acceptance criteria, and can be used as a surrogate for further bioequivalence studies; it is also recommended by regulatory authorities.
2. For the optimum design of a modified release oral dosage form, the key step is to understand the principles of GI dynamics such as gastric emptying, small intestinal transit, colonic transit, etc. Acquiring knowledge about the rate and extent of drug absorption from different sites of GI tract, and factors that can alter one limit the absorption further aid in designing the type of dosage form that is needed for a particular drug.
3. For instance, with drugs such as sulpiride, furosemide, theophylline and albuterol which are predominantly absorbed from the upper part of the GI tract, designing a gastro

retentive dosage form is a logical strategy for improving and extending their limited oral bioavailability. With the advent of g-scintigraphy, it is now possible to understand the various physiological and pharmaceutical factors involved in oral drug delivery.

4. One of the most reliable and novel approaches includes the use of the InteliSiteE Capsule, which provides quick assessment of the oral absorption of drugs within specific regions of the GI tract.
5. The method is simple, operator-controlled, noninvasive, and leads to cost-effective development of novel oral PDDS.

Table 2: Parameters Used In IVIVC correlation.[44]

Level	In Vitro	In Vivo
A	Dissolution curve	Absorption Curves
B	Statistical moments: MDT	Statistical moments: MRT, MAT, etc
C	Disintegration time, Time to have 10,50,90% dissolved, Dissolution rate, Dissolution efficiency	C max, T max, Ka, Time to have 10,50,90% absorbed, AUC (total of cumulative)

Table 3: Evaluation parameters of PDDS Tablet oral dosage form.[45]

Evaluation of preformulation parameters	Evaluation of tablet properties
Angle of repose, Determination of Bulk Density Tapped Density, Hausner's Ratio, Carr's index	Weight variation Tablet Hardness, Friability, Tablet Thickness, Content Uniformity, Disintegration time

Recent advances in the PDDS

Table 4: Advantages of Technology.

Technology	Mechanism	Proprietary name and Dosage form	API	Disease	Advantage
OROS	Osmotic mechanism	Covera-HS®; XL Tablet	Verapamil HCl	Hypertension	Prevent the dangerous surge of BP in the early morning
CODAS	Multiparticulate, pH dependent system	Verelan® PM; XL Release Capsule	Verapamil HCl	Hypertension	Early morning peaks plasma concentration after bed time dosing
DIFFFUCAPS	Multiparticulate system	Innopran®; XL Release tablets	Propranolol HCl, Verapamil HCl	Hypertension	Lag time is 4-5 hours. Release is pH independent
THREE DIMENSIONAL PRINTING	Externally reglated system	TheirForm®	Diclofenac Sodium	Inflammation	Complex, computer generated delivery system.
CONTIN®	Extended release tablet	Uniphyl® extended release tablet	Theophylline	Asthma	Early morning Peak plasma concetration following by bed time dosing
IPDAS	Multiparticulate system	Naprelan®	Naproxen sodium	Acute and Chronic pain	Controlled release in GIT Independent of the feeding system

CONCLUSION

- In last two decades a number of modern technologies including targeting concept have egg merged for successful oral controlled delivery of various bio-activities. The limitations have been overwhelmed by these modern technologies, which are providing effective local as well as systemic drug levels at desirable sites with improve safety profiles. The matrix, ion exchange, floating and bioadhesive concept have been developed and explored for controlled and pulsatile oral delivery.
- Research involved the sophistication of designing oral controlled /sustained drug delivery system with modern targeting or site specific concept. The development in the bioengineering and cell biology provided newer dimensions designing and fabrication of oral system. The gastric retention time has been prolonged by using the buoyancy and bioadhesive principles; furthermore site-specific bioadhesion concept has been introduced to enhance the efficacy of the systems. By using these systems, the pre-systemic clearance of drugs can be avoided and drug can reach pre-selected site in intact form.
- The development in the *in vitro* and *in vivo* evaluation methods with the aid of modern scientific technologies provides necessary tools to make the *in vitro* dissolution test, which simulates *in vivo* condition more precise and decisive. For successful development of chronotherapeutic dosage form, knowledge of circadian time structure, rhythm in disease pathophysiology or 24 hr pattern in symptom intensity of chronic medical conditions, and chronospharmacology of medication is needed. Significant progress has been made toward achieving PDDS that can effectively treat diseases with non constant dosing therapy.

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