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Pulsatile Drug Delivery System–A Review

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Abstract

Pulsatile drug delivery systems are attaining more and more interest in modern pharmaceuticals for the development of drugs for which conventional drugs with continuous release are not deal. In some instances where constant blood level of drugs is not desirable, in such cases pulsatile drug delivery system is advisable. These are designed such a way that complete and rapid drug release is achieved after lag time. Pulsatile drug delivery systems are classified into site specific where the drug releases at desired site within intestinal tract. Time controlled release in which drug release is controlled by the delivery system and not by the external environment. Site controlled release in which the drug release is controlled pH, or enzymes present in the intestinal tract. This review covers various pulsatile systems like capsular systems, osmotic systems, single and multiple systems based on use of soluble and erodible polymers coating and the current PDDS already available in the market.

Keywords: Pulsatile drug delivery systems, Single unit, Multiple units.

Contents

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1. Introduction

Timed-release formulations are designed to release a drug at a pre-determined time (the lag time) after administration. Orally administered timed-release dosage forms have been widely investigated for use in chronopharmacologic therapy, in site-specific drug delivery, in peptide drug absorption enhancement, and in avoiding pharmacokinetic drug–drug interactions. However, timed-release dosage forms often have poor bioavailability compared to immediate-release conventional dosage forms. This effect is thought to result from poor dissolution and absorption of the drug in the lower gastrointestinal (GI) tract, most commonly the ileum and the colon. Several timed-release technologies have been described. These include use of a rupturable coating that surrounds multiple pellets loaded with the drug a compression-coated soluble barrier that erodes, surrounding a single unit-core tablet containing the drug; and a swellable hydrogel plug which dislodges when swollen, set into a water-insoluble capsule body filled with the drug of these formulations, compression-coated tablets are among the simplest to manufacture. Compression-coated tablets are composed of an inner

core that contains an active pharmaceutical ingredient surrounded by an outer layer that slowly dissolves or disintegrates to make a lag time of drug release. A time-release formulation could allow drug release and a greater plasma drug concentration at the point in the circadian cycle when clinical signs develop or increase.

2. Description

1. Time controlled Pulsatile release system
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   1.2. Multi-particulate system
2. Inflammation-induced pulsatile release
   2.1 Drug release from intelligent gels responding to antibody1 concentration
   2.2 pH sensitive drug delivery system
3. External stimuli pulsatile release
   3.1. Electro responsive pulsatile release
   3.2. Magnetically induced pulsatile release
4. Pulsatile release systems for vaccine and hormone products

1. **Time controlled pulsatile release system**

These time-controlled systems can be classified as single unit (e.g., tablet or capsule) or multiple unit systems. These systems consist of an outer released controlling water insoluble but permeable coating subject to mechanically induced rupture phenomenon. Recently these systems are based on core tablet form and hard gelatin form were described in recent days, all coated by inner swellable and outer rupturable layer. The film layer ruptures and may be attained by including swelling, osmotic effervescent additives in the reservoir (Krogel & Bodmeier, 1999).

1.1 Single unit systems - Capsular Systems

Different single-unit capsular PDDS have been developed (Fig 2). A general design for capsular systems consists of an insoluble capsule body housing a drug and a plug. After a predetermined time lag due to swelling, erosion, dissolution the plug is removed. The Pulsincap® system is an

Good example of such a system the body is made up of a water-insoluble capsule and body is filled with drug formulation. Then the body is closed at the open end with a swellable hydrogel plug. Upon contact with gastro-intestinal fluids or dissolution medium, the plug swells, then it pushes itself out of the capsule after a lag time. This is followed by a spur-of-the-moment release of the drug. The time lag can be controlled by changing the dimension and the position of the plug. For water insoluble drugs, a spontaneous release can be ensured by insertion of effervescent agents or disintegrates. 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, 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.

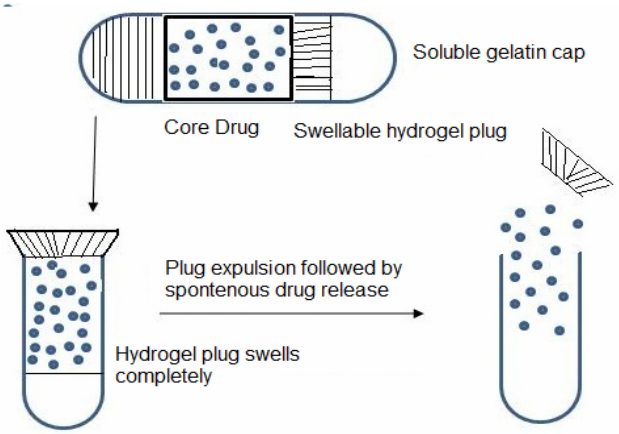

Fig.1 Schematic diagram of capsular system

Capsular system based on Osmosis - 'PORT' System

The Port System consists of a gelatin capsule it is coated with a semi permeable membrane (e.g: cellulose acetate) covering an insoluble plug (e.g: lipidic) and an osmotically active agent along with the drug formulation. When the aqueous medium comes in contact, the water starts diffuses across the semi permeable membrane, ensuing in

enlarged inner pressure that ejects the plug after a lag time phase. The time lag is controlled by the thickness of semi permeable membrane. It shows good correlation in lag times of *in-vitro* and *in-vivo* experiments in humans.

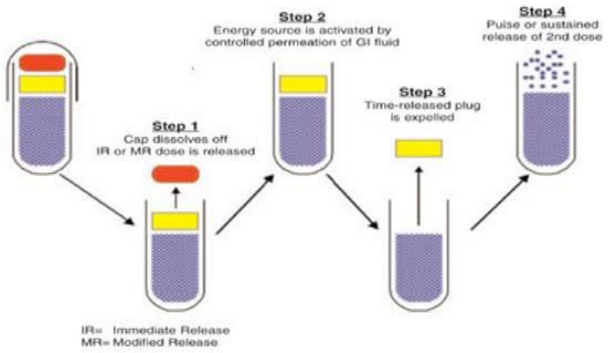

Fig.2 Capsular system based on Osmosis port System

To deliver this type of the drug in liquid form, an osmotically driven capsular system was developed. In this system, the liquid drug is absorbed very highly into porous particles, then the drug is released through an orifice of a semi permeable capsule supported by an expanding osmotic layer after the barrier layer is dissolved. In this system, the drug is delivered by the capsule's osmotic infusion of moisture from the body. The capsule wall is made up of elastic material is an orifice. As the osmosis proceeds, the pressure within the capsule raises more, then it leads wall to stretch. when the elastic wall relaxes the orfice is small and stops the flow of the drug through the orifice essentially stops, but when the elastic wall swollen away from threshold value, the orifice expand adequately to allow drug release at a essential rate. Elastomers, such as styrene-butadiene copolymer have been recommended.

Delivery by series of stops

This delivery system describes about implantable capsules. The capsule contains water-absorptive osmotic engine and drug is placed in the compartments and it is separated by a movable separation. The pulsatile delivery is achieved by a series of stops along the inner wall of the capsule. These stops block the movement of the partition but are prevail over in series as the osmotic pressure rises on top of a threshold level. The number of stops and the longitudinal placements of the stops along the length of the capsule states the number and frequency of the pulses, and the arrangement of the separation controls the pulse intensity. This system was used to deliver porcine somatotropin.

Delivery by reservoir systems with erodible or soluble barrier coatings

Most of the pulsatile drug delivery systems are reservoir devices. These are coated with a barrier layer. This barrier erodes or dissolves after a specific lag time period, and the drug is subsequently released hastily. The time lag depends on the thickness of the coating layer. *The Time Clock® system* consists of solid dosages form coated with a lipid barriers containing carnauba wax and bees wax beside with surfactants, such as polyoxy ethylene 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. The major advantage of this system is it's easy to manufacture without any need of special equipments. The disadvantage of this system is a premature drug release when the penetrating water dissolves the drug. *The Chronotropic® system* The system is suitable for both tablets and capsule formulations *It* consists of a drug-containing core coated by hydrophilic swellable hydroxypropylmethyl cellulose (HPMC), which is responsible for a lag phase in the onset of drug release. Lag time is controlled by the thickness and the viscosity grades of HPMC used in coating the drug core.

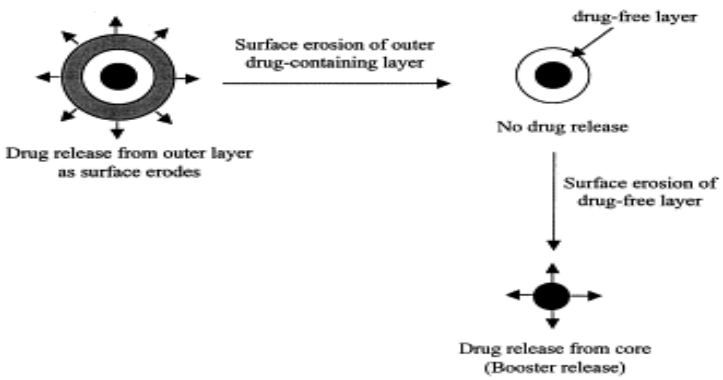

Fig.3 Delivery by reservoir systems with erodible or soluble barrier coatings

1.2. **Multiparticulate Systems**

Multi-particulate drug delivery systems are oral dosage forms consists of a multiplicity of small distinct units, the active substance is present in a number of small independent subunits. They afford many advantages over single-unit systems because of their small in size, less inter and intra-subject variability in gastrointestinal transit time, reduced adverse effects and better acceptability, no risk of dose dumping, flexibility in design and finally Improve stability, The draw backs in this system are which include lack of manufacturing, reproducibility, high cost of production, multiple formulation steps and also the need of advanced technologies.

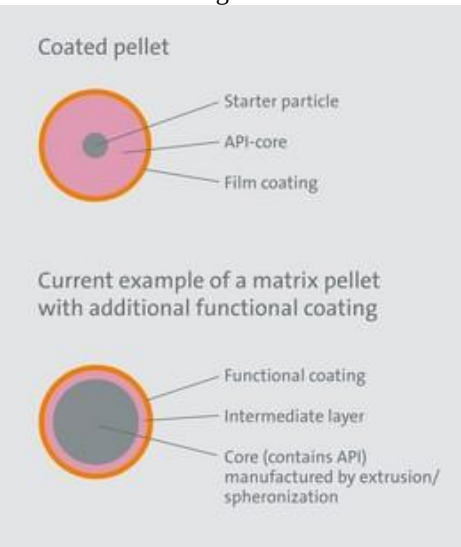

Fig.4 Multiparticulate Systems

Pulsatile System Based on Rupturable Coating

This is a multi particulate 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 super disintegrants like, sodium starch glycollate, L-hydroxypropyl cellulose, sodium carboxymethyl cellulose etc. Upon opening of water, the swelling layer expands, ensuing in rupture of film with succeeding fast drug release. The drug release is independent to environmental factors like pH and drug solubility. The lag time phase can be varied by varying coating thickness or adding high amounts of lipophilic plasticizer in the outermost layer.

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 then the core displaces the lipid material. After the reduction of lipid material, internal pressure increases until a critical stress is reached, which results in rupture of the coating material. Another system is based on a capsule or tablet composed of a large number of pellets consisting of two or more pellets or part.

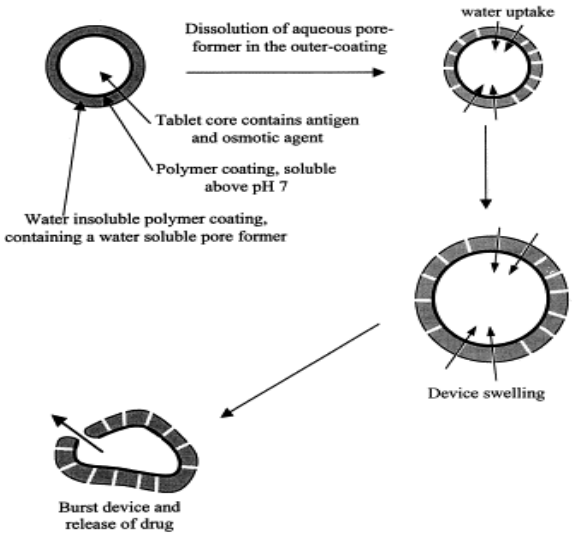

Fig.5 Time controlled expulsion system

Pulsatile Delivery by Change in Membrane Permeability

The permeability and water uptake of acrylic polymers with quaternary ammonium groups can be inclined by the presence of altered counter-ions in the medium. Numerous 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 it facilitates the interaction of polymer with water, thereby changing its permeability and allowing water to permeate the active core in a controlled manner.

Sigmoidal Release System

This system consists of pellet cores comprising drug and succinic acid coated with ammonio-methacrylate copolymer USP/NF type B. The lag time controls the rate of water influx through the polymer membrane. The water dissolves acid and the drug in the core. The different types of acids that can be used include glutaric acid, tartaric acid, malic acid, citric acid succinic acid, acetic acid.

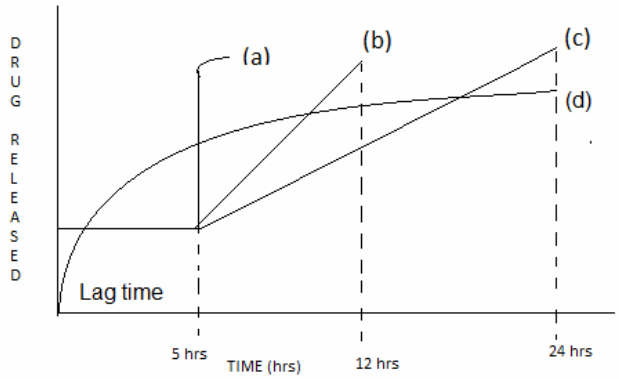

Fig. 6 Schematic representation of different drug delivery systems where (a) = sigmoidal release after lag time, (b)= delayed release after lag time, (c) = sustained release after lag time, (d) = extended release without lag time

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.

2. Inflammation-induced pulsatile release

On delivery of any physical or chemical stress, such as injury, fracture etc., inflammation takes place at the injured sites. Throughout irritation, hydroxyl radicals are produced from these inflammation-responsive cells. Degradation via hydroxyl radicals yet, is usually dominant and hasty when Hyaluronic Acid gel is injected at seditious sites. Thus, it is likely to treat patients with inflammatory diseases like rheumatoid arthritis, using anti-inflammatory drug integrated HA gels as new implantable drug delivery systems.

2.1 Drug release from intelligent gels responding to antibody1 concentration

There are various kinds of bioactive compounds which are present in the body. In recent times, novel gels were developed which responded to the change in concentration of bioactive compounds to vary their swelling/deswelling features. Special interest was given to antigen-antibody complex formation as the cross-linking units in the gel, since such interaction is very unambiguous. Utilizing the disparity in association constants between the polymerized antibodies and naturally derived antibodies in the direction of specific antigens, reversible gel swelling/deswelling and drug permeation changes occurs.

2.2. pH sensitive drug delivery system

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

3. External stimuli pulsatile release: This system was divided into three subparts.

3.1. Electro responsive pulsatile release

These delivery systems are prepared from polyelectrolyte's and they are pH-responsive as well as electro-responsive. Examples of naturally occurring polymers include xanthan gum and calcium alginate, hyaluronic acid,

chondroitin sulphate, agarose, carbomer. The synthetic polymers are generally used are acrylate and methacrylate derivatives such as partially hydrolyzed poly acrylamide, poly dimethyl aminopropyl acrylamide .

Micro electro mechanical systems (MEMS)

A micro fabricated device having capability to store up and release multiple chemical substances on require by a mechanism devoid of moving its parts. The digital capability of MEMS may allow larger temporal control over drug release when compared to traditional polymer-based systems. Another advance development used in MEMS technology is the microchip. The microchip consists of an arrangement of reservoirs that expand through an electrolyte-impermeable substrate. The prototype microchip is made up 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 packed with any combination of drug or drug mixtures in any form (i.e. solid, liquid or gel). When the 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. Such as simultaneous constant and pulsatile release complexes can be achieved from the microchips. Microchip has the ability to control both release time and release rate.

3.2. Magnetically induced pulsatile release

The use of oscillating magnetic field is to modulate the rates of drug release from polymer matrix was one of the old methodologies. Magnetic carriers receive magnetic response to a magnetic field from incorporated materials such as, Iron, Nickel, Cobalt, Magnetite etc. For biomedical applications, magnetic carriers are 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.

4. Pulsatile release systems for vaccine and hormone products

Vaccines are conventionally administered as preliminary shot of an antigen followed by repeated immunization shots to generate shielding immunity. The frequency of the booster shots, and hence the exact immunization-schedule is antigen dependent. Also, co-administration of vaccine adjuvant is frequently required to improve the immune response to achieve protective immunity. PDDS tender the opportunity 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.

Recent techniques used in Pulsatile Drug Delivery system

1. Spheroidal Oral Drug Absorption System (SODAS)® Technology

SODAS® is Elan's Multiparticulate drug delivery system. SODAS® technology is characterized by its inherent flexibility, based on the production of controlled release beads enabling the production of customized dosage forms that respond directly to individual drug candidate needs. Elan can provide a number of drug release profiles, including immediate release of drug followed by sustained release to give rise to a fast onset of action, which is maintained for 24 hours. pulsatile release, is the additional option where a once daily dosage form can resemble multiple daily doses by releasing drug in discrete bursts throughout the day. Elan's SODAS® Technology is based on the production of uniform spherical beads of 1-2 mm in diameter containing drug plus excipients and coated with product specific controlled release polymers. The most recent regulatory approvals for a SODAS® based system occurring with the launch of once-daily oral dosage forms of Avinza™, Ritalin® LA and Focalin® XR.

2. The Intestinal Protective Drug Absorption System (IPDAS)® Technology

IPDAS Technology is a new oral drug delivery approach that is applicable to gastrointestinal (GI) irritant drugs, including (NSAID) class. In a tablet dosage form multiparticulate technology is employed in this IPDAS delivery system. It consists of number of high density controlled beads which are compressed into tablet form. Once an IPDAS® tablet is ingested, it disintegrates and disperses beads containing a drug in the stomach, which passes into the duodenum along the gastrointestinal tract in a controlled and gradual manner, independent of feeding state. The polymer system used to coat the beads and/or the micro matrix of polymer/active ingredient formed in the extruded/spheronised multiparticulates is responsible for the controlled release of active ingredient. The intestinal protection of IPDAS® technology is inherent by virtue of the multiparticulate nature of the formulation, which ensures wide dispersion of irritant drug throughout the gastrointestinal tract. IPDAS® was initially designed as part of the development process for Elan Drug Technologies' proprietary naproxen formulation, Naprelan®. Acid or the sodium salt of naproxen although has consistent pharmacokinetic characteristics with once-daily dosing. A large bolus dose of naproxen precludes safe use of an immediate-release form due to GI irritant and ulcerogenic potential. In addition, the desired pharmacodynamic activity of a once-daily dosage form of naproxen requires rapidly available naproxen for a prompt onset of analgesic activity as well as a prolonged phase of absorption to provide 24 h analgesic/anti-inflammatory activity. The main objective is to reduce gastric irritancy in-once daily controlled release system with fast onset of action. This was achieved in Naprelan® the onset of pain relief is within 30mins and lasts upto 24hours and has been well tolerated.

3. Chrono therapeutic Oral Drug Absorption System CODAS™ Technology

A delayed drug action is required for certain variety of reasons. Chronotherapy is an example of this type where drug release is to be prolonged after administration. This technique was developed to achieve prolonged interval of drug release after administration (circadian pattern). Controlled onset, and extended release delivery system are some of the advantages of this CODAS technology. Drug release rate is independent of pH, posture and food.

Verelan® PM is the commercial product of CODAS technology. It is designed as bed time dosing, incorporating 4 to 5 hours in drug delivery after ingestion. This delayed drug delivery is due to the introduced level of non-enteric release controlling polymers (a combination of water soluble and water insoluble polymer) applied to the drug loaded beads. A water soluble polymer slowly dissolves when the beads come in contact with water in gastrointestinal tract. Then the water soluble polymers slowly dissolve and the drug diffuses through pores. Controlled release of drug is maintained by water insoluble polymers which act as a barrier. Maximum plasma of verapamil is achieved at morning times.

4. Programmable Oral Drug Absorption System (PRODAS®) Technology

PRODAS technology combines the benefits of tabletting with in a capsule. In this PRODAS delivery system a hard gelatin capsule is used with in which many number of mini tablets are incorporated. This technique is flexible enough that one can preprogram the release rate of the drug. Each mini tablet is formulated individually and programmed to release the drug at different sites within gastro intestinal track. High drug loading is possible by using sizes of mini tablets. This technique resembles the characteristics of different conventional dosage forms by means of mini tablets.

5. Time Multiple Action Delivery system (TMDS) Technology

TMDS Technology provide control release rate of multiple ingredient within single tablet in programme manner. TMDS Technology allows for more than one active ingredient in a single tablet formulation provide multiple release profile over extended period of time. [10, 11]

6. Dividable Multiple Action Delivery System (DMDS) Technology

DMDS is designed to provide greater dosing flexibility that improve product efficacy and reduces side effects. Once broken, traditional controlled release tablet lose their controlled release mechanism of delivery. But in DMDS technology when the tablet broken down in half each respective portion will achieve exactly the same release profile as that of the whole tablet. This allows the patient and physician to adjust the dosing regimen according to the clinical needs without compromising efficacy.

7. Programmed Multiple-action Delivery System (PMDS) Technology

PMDS technology as compared to other PDDS controlled released techniques, is a milti-phasic delivery system of active ingredients in more controlled pattern. In this technology active ingredients are released at predetermined time and desired levels are obtained at consistent basis. Achieving uni formity of dose and reproducibility are the two advantages of this PMDS technology. It is designed to produce greater flexibility of dosing that results in product efficacy and reduces side effects.

8. GEOCLOCK® Technol

Geoclock® is the preparation of chronotherapy-focused press-coated tablets which have an active drug inside an outer tablet layer consisting of a mixture of hydrophobic wax and brittle material in order to obtain a pH-independent lag time prior to core drug delivery at a predetermined release rate. This dry coating approach designed to allow periodic release of both slow release and immediate release active cores by releasing the inner table first after which time the surrounding outer shell gradually disintegrates.

As well as controlled release, the Geoclock® technology also has applications for the improved release of colonic drug delivery, as well as multiple pulse drug delivery to deliver doses of the drug at specific times throughout the day. Using this GEOCLOCK novel technology, SkyePharma has been developing Lodotra™, a rheumathoid arthritis drug, on behalf of Nitec Pharma. Lodotra™ will deliver the active pharmaceutical ingredient at the most suitable time of day.

.9. GEOMATRIX™ Technology

The Geomatrix™ technology is applied to achieve customised levels of controlled release of specific drugs and from a single dosage form to achieve simultaneous release of two different drugs at different rate. The controlled release is achieved by multilayered tablet made of two basic key components; 1) hydrophilic polymers such as hydroxy propyl methycellulose (HPMC) and 2) surface controlling barrier layers. A barrier layers controls the drug release from the active loaded core surface upon exposure to the fluid. The combination of layers, each with different rates of swelling, gelling and erosion, is responsible for the rate of drug release within the body. The drug concentration is high when swallowed but the surface area is low. As time progresses the core swells and drug concentration decreases upon increase in surface area.

One of the major benefits of the Geomatrix™ technology is its ability to be easily incorporated into the production line. The Geomatrix™ tablets can be manufactured by readily available equipment that can be integrated into widely-used pharmaceutical processes, thus giving firms more control over their own production activities. Other advantages of the Geomatrix™ technology are Reproducibility, Efficacy, Versatility of release control mechanisms,

Controlled release of poorly soluble drugs, Timed release of drugs, Bi-phasic release of drugs, Release of 2 or more drugs at different rates, Pulsed release of drugs, Safety of use SkyePharma manufactures several Geomatrix™ products for its partners, which include Sular® for Sciele, ZYFLO CR™ for Critical Therapeutics, Coruno® for Therabel, diclofenac-ratiopharm® uno for ratiopharm and Madopar DR® for Roche.

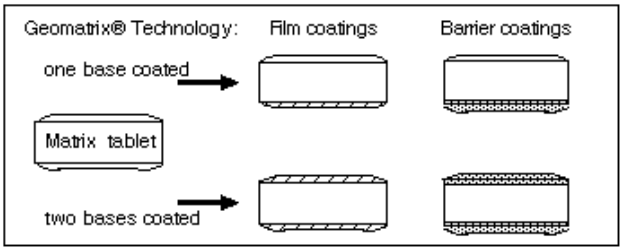

Fig.7 Geomatrix Technology: two- and three-layer systems

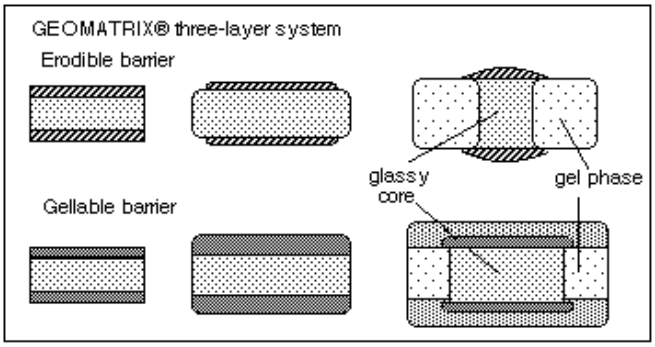

Fig.8 Swelling behaviour of the Geomatrix three-layer systems with the different types of barrier coatings: erodible or gellable

10. PULSYS Technology

MiddleBrook (also known as Advancis Pharmaceuticals) Pharmaceuticals developed PULSYS, is once a day pulsatile delivery technology. The PULSYS dosage form is a compressed tablet that contains pellets designed to release drug at different regions in the gastro-intestinal tract in a pulsatile manner. The dosage form consists of multiple pellets of varying release profiles that are combined in a proportion so as to produce a constant escalation in plasma drug levels in the early portion of the dosing interval. The transit properties of pellets enhance the overall absorption-time window and offer improved bioavailability compared to tablet matrix forms. Moxatag™ tablet contain Amoxicillin is designed as PULSYS Technology to deliver amoxicillin at lower dose over a short duration therapy in once daily formulation. Advancis have also demonstrated that by preclinical studies which improved bactericidal effect for amoxicillin when deliver in pulsatile manner as compared to standard dosing regimen even against resistant bacteria.

11. One step dry coating Technology (OSDrC) Technology

The OSDrC® rotary tabletting machine supports single-step manufacturing of pharmaceutical products with its variable double-punch configuration. This machine is ideal for manufacturing a variety of drug products with high quality and low cost. This innovative technology can also replace conventional sugar- and film-coated tablets. By this technique production scientist devises new novel dosage forms and align capability with scientific creativity

3. Conclusion

Presently, oral delivery of drug is still by far the most preferable route of drug delivery due to the ease of administration, patient compliance and flexibility in its formulations. A significant progress has been made toward achieving PDDS that can effectively treat diseases with non-constant dosing therapies. Various pulsatile technologies are researched and some are currently in the market.

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