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A REVIEW: CURRENT REPORTED TECHNOLOGIES USED IN PULSATILE DRUG DELIVERY SYSTEM

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ABSTRACT

Pulsatile drug delivery systems (PDDS) gaining importance as it is offers a more sophisticated approach to traditional drug delivery. Pulsatile systems deliver the drug at the right site of action at the right time and in the right amount, thus providing spatial and temporal delivery and increasing patient compliance.There are certain conditions for which continuous conventional controlled release pattern is not suitablediseases like Peptic ulcer, Asthama, Cardivascular disease rheumatoid arthritis. This review covers different pharmaceutical technologies used in development of pulsatile drug delivery systems.

Keywords: Pulsatile drug delivery system, Chronopharmacotherapy, P ulsatile drug delivery technologies.

INTRODUCTION

Controlled drug delivery systems have acquired a center stage in the arena of pharmaceutical R&D business. Such systems offer temporal and/or spatial control over the release of drug and grant a new lease of life to a drug molecule in terms of patentability**.** These dosage forms offer many advantages, such as nearly constant drug level at the site of action, prevention of peak-valley fluctuations, reduction in dose of drug, reduced dosage frequency, avoidance of side effects, and improved patient compliance. The oral controlled-release system shows a typical pattern of drug release in which the drug concentration is maintained in the therapeutic window for a prolonged period of time (sustained release), thereby ensuring sustained therapeutic action. Thus, the release commences as soon as the dosage form is administered as inthe case of conventional dosage forms [1, 2].

There are certain conditions for which continuous conventional controlled release pattern is not suitable. These conditions demand release of drug after a lagtime. Therefore chronopharmacotherapy requirepulsatile delivery diseaseslike Peptic ulcer, Asthama, Cardiovascular disease rheumatoid arthritis.

by a lag time that is an interval of no drug release followed by rapid drugrelease. The first pulsed delivery formulation that released the active substance at aprecisely defined time point was developed in the early 1990s. In this context, the aimof the research was to achieve a so-called sigmoidal release pattern. The characteristicfeature of the formulation was a defined lag time followed by a drug pulse with theenclosed active quantity being released at once [3] (Figure 1. shows Drug release profile of pulsatile drug delivery).

CURRENTLY REPORTED SYSTEMS

Pulsatile systems are basically time-controlled drug delivery systems in which the system controls the lag time independent of environmental factors like pH, enzymes, gastro-intestinal motility, etc. These time-controlled systems can be classified as single unit (e.g., tablet or capsule) or multiple unit (e.g., pellets) systems.

SINGLE UNIT SYSTEM

CAPSULAR SYSTEMS

Different single-unit capsular pulsatile drug delivery systems have been developed. A general architecture of such systems consists of an insoluble capsule body housing a drug and a plug. The plug is removed after a predetermined lag time owing to swelling, erosion, or dissolution.

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PULSINCAP SYSTEMS

The Pulsincap® system is made up of a water-insoluble capsule body filled with drug formulation**.** The body is closed at the open end with a swellable hydrogel plug. Upon contact with dissolution medium or gastro-intestinal fluids, the plug swells, pushing itself out of the capsule after a lag time. This is followed by a rapid drug release. Manipulating the dimension and the position of the plug can control the lag time. For water-insoluble drugs, a rapid release can be ensured by inclusion of effervescent agents or disintegrants [4]. (Figure 2 shows Pulsatile release from an insoluble capsule body.) The plug material consists of insoluble but permeable and swellable polymers (eg, polymethacrylates), erodible compressed polymers (eg, hydroxypropylmethyl cellulose, polyvinyl alcohol, polyethylene oxide), congealed melted polymers (eg, saturated polyglycolated glycerides, glycerylmonooleate), and enzymatically controlled erodible polymer (e.g. pectin). These formulations were well tolerated in animals and healthy volunteers, and there were no reports of gastro-intestinal irritation. However, there was a potential problem of variable gastric residence time, which was overcome by enteric coating the system to allow its dissolution only in the higher pH region of small intestine.

PORT® SYSTEMS

The Port® System consists of a gelatin capsule coated with a semi permeable membrane (eg, cellulose acetate, PGLA) housing an insoluble plug (eg, lipidic) and an osmotically active agents (NaHCO3, Citric acid) along with the drug formulation. When in contact with the aqueous medium, water diffuses across the semi permeable membrane, resulting in increased inner pressure that ejects the plug after a lag time. Coating thickness controls the lag time. The system was proposed to deliver methylphenidate for the treatment of attention deficit hyperactivity disorder (ADHD) in school-age children. Such a system avoids a second daily dose that otherwise would have been administered by a nurse during school hours [5]. (Figure 3 shows PORT® SYSTEM.)

A SYSTEM BASED ON EXPANDABLE ORIFICE

To deliver the drug in liquid form, an osmotically driven capsular system was developed in which the liquid drug is absorbed into highly porous particles, which release the drug through an orifice of a semi permeable capsule supported by an expanding osmotic layer after the barrier layer is dissolved**.** 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 is distended beyond threshold value, the orifice expands sufficiently to allow drug release at a required rate. Elastomers,such as styrene-butadiene copolymer have been suggested. Pulsatile release was achieved after lag times of 1 to 10 hours, depending on the thickness of the barrier layer and that of semipermeable membrane, and a capsule designed for implantation can deliver drug intermittently at intervals of 6 hours for 2 days [6].

DELIVERY BY A SERIES OF STOPS

The implantable capsules containing a drug and a water-absorptive osmotic engine 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 pulseintensity. This system was used to deliver porcine somatotropin [7].

PULSATILE DELIVERY BY SOLUBILITY MODULATION

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. These values show that the solubility of the drug is function of the modulator concentration, while the modulator's solubility is largely independent of drug concentration. The modulating agent can be a solid organic acid, inorganic salt, or organic salt. In order to control zero-order release period and commencement of pulsed release, ratio of drug/modulator can be varied. After the period of zero-order release, the drug is delivered as one large pulse [8-10].

PULSATILE SYSTEMS WITH ERODIBLE OR SOLUBLE BARRIERCOATING

Most of the pulsatile drug delivery systems are reservoir devices coated with a barrier layer. This barrier erodes or dissolves after a specific lag period, and the drug is subsequently released rapidly. The lag time depends on the thickness of the coating layer.

TIME CLOCK® SYSTEMS

The Time Clock® system consists of a solid dosage form coated with lipidic barriers containing carnuba wax and bees' wax along with surfactants, such as polyoxyethylenesorbitanmonooleate**.** 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. Such systems are better suited for water-soluble drugs. The major advantage of this system is its ease of manufacturing without any need of special equipment. However, such lipid-based systems may have high in-vivo variability (eg,food effects) [11].

CHRONOTROPIC® SYSTEMS

The Chronotropic® system consists of a drug-containing core coated by hydrophilic swellablehydroxypropylmethyl cellulose (HPMC), which is responsible for a lag phase in the onset of release**.** In addition, through the application of an outer gastric-resistant enteric film, the variability in gastric emptying time can be overcome, and a colon-specific release can be obtained, relying on the relative reproducibility of small intestinal transit time**.** The lag time is controlled by the thickness and the viscosity grades of HPMC [12,13].

MULTILAYERED TABLET

A release pattern with two pulses was obtained from a three-layered tablet containing two drug containing layers separated by a drug-free gellable polymeric barrier layer. This three-layered tablet was coated on three sides with in impermeable ethyl cellulose, and the top portion was left uncoated. Upon contact with dissolution medium, the initial dose incorporated into the top layer was released rapidly from the non-coated surface. The second pulse was obtained from the bottom layer after the gelling barrier layer of HPMC was eroded and dissolved. The rate of gelling and/or dissolution of the barrier layer control the appearance of the second pulse. The gelling polymers reported include cellulose derivatives like HPMC, methyl cellulose, or polyvinyl alcohols of various molecular weights and the coating materials include ethyl cellulose, cellulose-acetate-propionate, methacrylic polymers, acrylic and mehtacrylic co-polymers, and polyalcohols.eg Geomatrix technology [14,15] (Figure 4. shows Multilayer tablet).

PULSATILE SYSTEMS WITH RUPTURABLE COATING

The effervescent excipients, swelling agents, or osmotic pressure can achieve the pressure necessary for the rupture of the coating. An effervescent mixture of citric acid and sodium bicarbonate was incorporated in a tablet core coated with ethyl cellulose. The carbon dioxide developed after penetration of water into the core resulted in a pulsatile release of drug after rupture of the coating. The release may depend on the mechanical properties of the coating layer**.** The highly swellable agents, also called superdisintegrants, are used to design a capsule-based system comprising a drug, swelling agent, and rupturable polymer layer**.** Examples of superdisintegrants include cross carmellose, sodium starch glycolate, and low substituted hydroxypropyl cellulose. The swelling of these materials resulted in a complete film rupture followed by rapid drug release. The lag time is function of the composition of the outer polymerlayer. The presence of hydrophilic polymer like HPMC reduces the lag time. The system can be used for delivery of both solid and liquid drug formulations. A reservoir system with a semipermeable coating was designed for delivery of drugs that exhibit extensive first-pass metabolism. The release pattern was similar to that obtained after administration of several immediate-release doses [16, 17]. Figure 5 shows Delivery systems with rupturable coating layer and erodible coating layers.

MULTIPARTICULATE SYSTEMS

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

PULSATILE SYSTEM BASED ON RUPTURABLE COATING

Time-Controlled Explosion System (Fujisawa Pharmaceutical Co., Ltd.)

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 [18, 19]. The swelling agents used include superdisintegrants like sodium carboxymethyl cellulose, sodium starch glycollate, L-hydroxypropyl cellulose, polymers like polyvinyl acetate, polyacrylic acid, polyethylene glycol, etc. Alternatively, an effervescent system comprising a mixture of tartaric acid and sodium bicarbonate may also be used. Upon ingress of water, the swellable layer expands, resulting in rupture of film with subsequent rapid drug release. The release is independent of environmental factors like pH and drug solubility. The lag time can be varied by varying coating thickness or adding high amounts of lipophilic plasticizer in the outermost layer. A rapid release after the lagphase was achieved with increased concentration of osmotic agent. *In-vivo* studies of time-controlled explosion system (TCES) with an *in-vitro* lag time of three hours showed appearance of drug in blood after 3 hours, and maximum blood levels after 5 hours [20].

OSMOTIC-BASED RUPTURABLE COATING SYSTEMS

Permeability Controlled System

This system is based on a combination of osmotic and swelling effects. The core containing the drug, a low bulk density solid and/or liquid lipid material (eg, mineral oil) and a disintegrant was prepared. This core was then coated with cellulose acetate. Upon immersion in aqueous medium, water penetrates the core displacing lipid material. After the depletion of lipid material, internal pressure increases until a critical stress is reached, which results in rupture of coating. The use of osmotically active agents that do not undergo swelling was reported by Schultz and Kleinebudde [21,22]. The pellet cores consisted of drug and sodium chloride. These were coated with a semipermeable cellulose acetate polymer. This polymer is selectively permeable to water and is impermeable to the drug. The lag time increased with increase in the coating thickness and with higher amounts of talc or lipophilic plasticizer in the coating. The sodium

chloride facilitated the desired fast release of drug. In absence of sodium chloride, a sustained release was obtained after the lag time due to a lower degree of core swelling that resulted in generation of small fissures.Chen has also proposed a system containing a core of drug and osmotically active agent (sodium chloride) coated with an insoluble permeable membrane[23].The coating materials reported include different types of poly (acrylate-methacrylate) copolymers and magnesium stearate, which reduces water permeability of the membrane, thus allowing for use of thinner films. Thicker films are to be avoided as they do not rupture completely. Using ethyl cellulose as a coating material, it was possible to affect lag time of enteric polymer to achieve rupturing after a predetermined time.

PULSATILE DELIVERY BY CHANGE IN MEMBRANE PERMEABILITY

The permeability and water uptake of acrylic polymers with quaternary ammonium groups can be influenced by the presence of different counter-ions in the medium. Several delivery systems based on this ion exchange have been developed. Eudragit RS 30D is reported to be a polymer of choice for this purpose. It typically contains positively polarized quaternary ammonium group in the polymer side chain, which is always accompanied by negative hydrochloride counter-ions. The ammonium group being hydrophilic facilitates the interaction of polymer with water, thereby changing its permeability and allowing water to permeate the active core in a controlled manner. This property is essential to achieve a precisely defined lag time. The cores were prepared using theophylline as model drug and sodium acetate. These pellets were coated using Eudragit RS30D (10% to 40% weight gain) in four different layer thicknesses. A correlation between film thickness and lag time was observed. After the lag time, interaction between the acetate and polymer increases the permeability of the coating so significantly that the entire active dose is liberated within a few minutes. The lag time increases with increasing thickness of the coat, but the release of the drug was found to be independent of this thickness and depended on the amount of salt present in the system.

SIGMOIDAL RELEASE SYSTEMS

This consists of pellet cores comprising drug and succinic acid coated with ammonio-methacrylate copolymer USP/NF type B. The lag time is controlled by the rate of water influx through the polymer membrane. The water dissolves succinic acid, and the drug in the core and the acid solution in turn increases permeability of the hydrated polymer film. In addition to succinic acid, acetic acid, glutaric acid, tartaric acid, malic acid, or citric acid can be used. The increased permeability can be explainedby improved hydration of film, which increases free volume [24, 25].

OTHER SYSTEMS

ENZYME CONTAINING CAPSULAR SHAPED

PULSATILE DRUG DELIVERY SYSTEMS

Krogel I. et al (1999) developed and evaluated an alternative pulsatile drug delivery system consisting of a drug containing, impermeable capsule body closed with an enzyme degradable plug. The degradation of plug material was not controlled by enzymes being present in the GIT, but by an enzyme being directly incorporated in the plug. The enzyme degradable plug consisted of the natural polysaccharide pectin, which is widely used in the food industry as a thickening agent and a pectinolytic enzyme mix. In this system pulsatile drug release is enzymatically controlled which is based on an impermeable capsule body which contains the drug and is closed by anerodible pectin / pectinase plug. (Figure 7 shows Schematic diagram of a one layer pulsatile DDS with an impermeable capsule body and pulsatile DDS with a two layer plug.) The powder (pectin and pectinolytic enzyme in different ratios) was blended and plug was prepared by direct compression with single punch press. The compressed plug was placed manually within the orifice of the drug filled poly (propylene) capsule body, with the top of the capsule body and the plug being even. The enzyme free layer of the two layers, plug was on the top of the capsule. The plug that consist of a mixture of enzyme degradable polymer and the enzyme, acts as release barrier. The polymer is degraded by enzyme after aqueous contact. Ideally no drug is released until the complete plug is degraded, leading to a defined lag time prior to the drug release. The two layer plug was prepared to separate the polymeric substance from the enzyme and to protect enzyme from the possibly degrading enzyme in GIT fluid. However, the lag time prior to drug release from the two layer DDS was longer than 6 hour and the subsequent drug release occurs in the sustained not in the pulsatile manner because the plug material was not completely emptied from the orifice. Hence one layered system is more important for study [26].

MODIFIED PULSINCAP TECHNIQUE

Murthy et al (2001) developed modified pulsincap preparation for rifampicin release studies of various hydrophilic polymers, such as Guar gum, Carbopol 940, Sodium alginate, HPMC, Methyl cellulose, Gum karaya and poly vinyl alcohol. Increase in the hydrophilic polymer content results in reduction in the release rate of the drug. Pulsincap was a patented preparation, consisting of hardened capsule body filled with basic drug mixture and sealed with hydrogel plug. After embedding sufficient amount of water the hydrogel plug will be released at predetermined time and the total content of the capsule will be released into the GIT fluids. Hence this preparation is regarded as time-release dosages form. In modified pulsincap, the drug polymer mixture is filled into the capsule body. The release rate of the drug was controlled by the formation of the viscous hydrogel within the capsule body. This technique controls the drug release rate whereas pulsincap preparation controls the drug release time [27].

CONFIGURATION OF TABLET MATRIX IN IMPERMEABLECYLINDER

A multifunctional drug delivery system based on HPMC matrices placed within an impermeable polymeric cylinder (open at both ends) was developed. Depending on the configuration of the device, extended release, floating or pulsatile drug delivery system could be obtained. This system can be of three types (Figure 8 shows Configuration of multifunctional matrix delivery system).

1. One drug-containing tablet within an impermeable cylinder.
2. Floating device (one tablet at each end of the cylinder with an air filled space inthe middle.
3. Pulsatile system (drug filled impermeable capsule half closed with an erodibledrug free plug).

The release behavior of the different devices was investigated as a function ofHPMC viscosity grade, HPMC content, type of drug, matrix weight, and position of thematrix within the polymer cylinder, addition of various fillers and agitation rate of therelease medium. Drug release increases with reduce HPMC viscosity grade, higheraqueous drug solubility, decrease HPMC content and increase surface area of thematrix. The release was fairly independent on the agitation rate, the position of thetablet within the polymeric cylinder and length of the cylinder. With the pulsatiledevice, the lag time prior to drug release could be controlled through the erosion rate ofthe matrix [28].

STIMULI INDUCED PULSATILE RELEASE
THERMO-RESPONSIVE HYDROGEL SYSTEMS

In closed-loop systems, or self-regulated systems, the release is indirect response to the conditions detected, be it temperature, type of solvent, pH, orconcentration. Poly (N-isopropylacrylamide) (PIPAAM) is a well-known example of athermo-responsive polymer. At its transition of 32oC, the polymer is soluble in water;but, as temperature is increased, the polymer precipitates and phase separates. Poly(ethylene glycol) and poly (propylene glycol) copolymers and poly (lactic acid) andpoly (glycolic acid) copolymers also exhibit thermo-responsiveness. These polymersare useful in developing thermo gelling systems (Atridox®); the drug is dissolved in theliquid form of the polymer at room temperature. When this mixture is injected in thebody, the polymer turns into a gel, which eventually degrades and releases the drugmolecules. Drug release from the PIPAAM hydrogel at temperature below32°C wasgoverned by diffusion, while above this drug release was stopped completely due toskin layer formation on the gel surface. Akihiko Kikuchi et al (2004) have recentlyreported a new method to accelerate gel swelling / deswelling kinetics based onmolecular design of the gel structure. Free mobile linear PIPAAM chains were graftedwithin the crossed linked PIPAAM hydrogels. The drug release profile from the grafttype PIPAAM gels were monitored after the immersion of the drug containing gels in asuitable release medium. Low molecular weight sodium salicylate was released in oneburst from conventional PIPAAM gels immediately after a temperature increased, afterwhich the release terminated due to formation of a dense impermeable skin layer on thesurface [29].

THERMORESPONSIVE POLYMERIC MICELLE SYSTEMS

Kataoka et al (2001) comprehensively reviewed the properties andbiological response of polymeric micelles making them the most noteworthy candidateas drug carrier for the treatment of cancer. The polymeric micelle is composed ofamphiphilic block copolymers exhibiting a hydrophobic core with a hydrophiliccorona. Due to this unique structure characteristic, polymer micelle exhibitscharacteristics that are not detected by the reticuloendothelial system (RES). Thus thepassive targeting could be achieved through a enhanced permeation retention effect ofthe tumor sites. Block co polymers formed micellar structure (with core shell structure) in aqueous solution below PIPAAM Tg temperature. The micelle formation wasconfirmed by dynamic light scattering measurements and LCST changes.

CHEMICAL STIMULI INDUCED PULSATILE RELEASE
GLUCOSE RESPONSIVE INSULIN RELEASE DEVICES

Self-regulating insulin-delivery devices depend on theconcentration of glucose in the blood to control the release of insulin. Ishihara et al(1983) prepared one gel membrane system to regulate the insulin permeability. Thesystem proposed immobilizing glucose oxidase (an enzyme) to a pH-responsivepolymeric hydrogel, which encloses a saturated insulin solution. At high glucoselevels, glucose is catalyzed by glucose oxidase and converts it to gluconic acid, thuslowering the pH. This decrease in pH causes the membrane to swell, forcing the insulinout of the device.

INFLAMMATION - INDUCED PULSATILE RELEASE

During inflammation, hydroxyl radicals (-OH) are produced fromthe inflammation responsive cells. Yui et al (1993) focused on the inflammatoryinduced hydroxyl radicals and designed drug delivery system, which responded tohydroxyl radicals and degraded in a limited manner. In the body hyaluronic acid (HA)is degraded either by specific enzyme, hyaluronidase, or hydroxyl radicals. Thus theyprepared crossed linked HA with ethylene glycol di-glyceride ether. Whenmicrospheres were incorporated in the HA hydrogel as a model drug, thesemicrospheres were released only when hydroxyl radicals induced HA gel degradation.Control HA gel implanted in the animals were relatively stable over a period of 100days. Thus it is possible to treat patients with inflammatory disease, such as rheumatoidarthritis, using anti-inflammatory drug incorporated HA gels as a new implantable drugdelivery system.

DRUG RELEASE FROM INTELLIGENT GELSRESPONDING TO ANTIBODY CONCENTRATIONS

There are numerous types of bioactive compounds, which existin the body. Recently, novel gels were developed which responded to the change inconcentration of bioactive compounds to alter their swelling/ deswelling characteristics.Miyata et al (1999) focused on the introduction of stimuli responsive cross-linkingstructure into hydrogels. A special attention was given to antigen antibody complexformation as the cross linking unit in the gel, because specific antigen recognition of anantibody can provide the basis for a new device fabrication. Utilizing the difference inassociation constants between polymerized antibodies and naturally derived antibodiestoward specific antigens, reversible gels swelling/ deswelling and drug permeationchanges occurred. Thus the biological stimuli responsive hydrogels were created.

Figure 1: Drug release profile of pulsatile drug delivery.

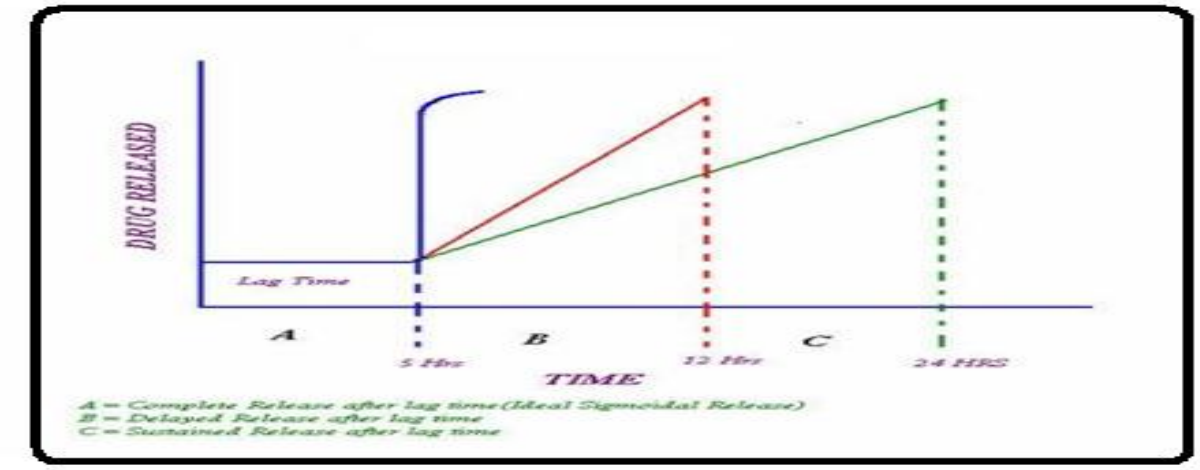


Figure 2: Pulsatile release from an insoluble capsule body. (Coated swellable plug; and Erodible plug Capsular System Based on Osmosis)

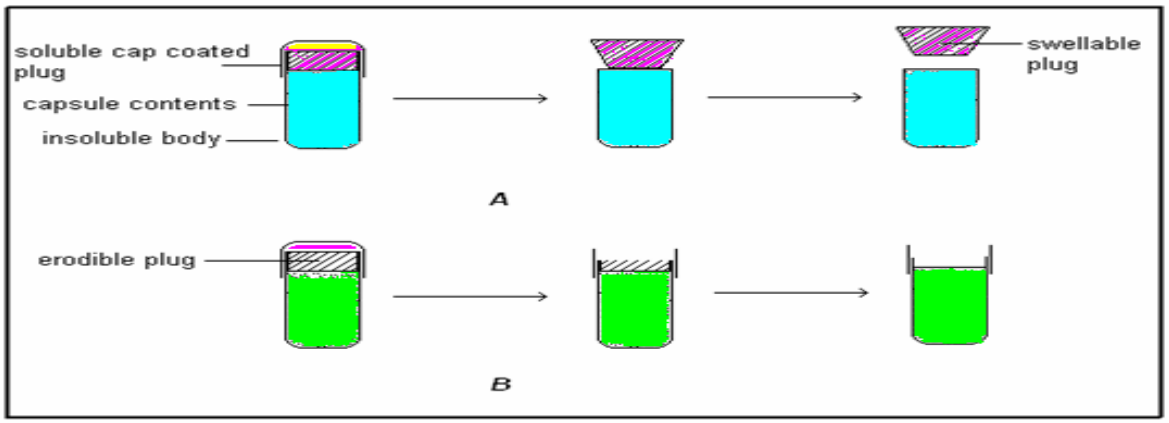


Figure 3:PORT® SYSTEM.

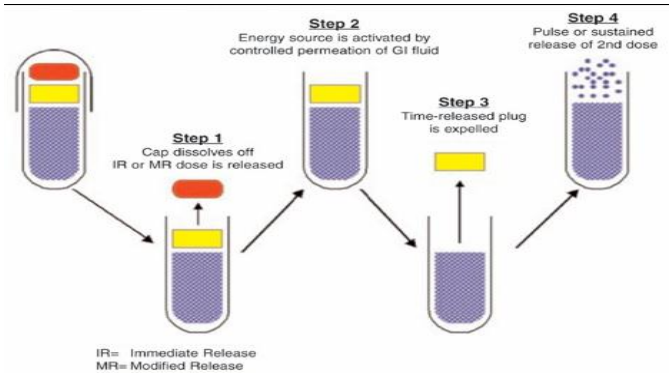


Figure 4: Multilayer Tablet.

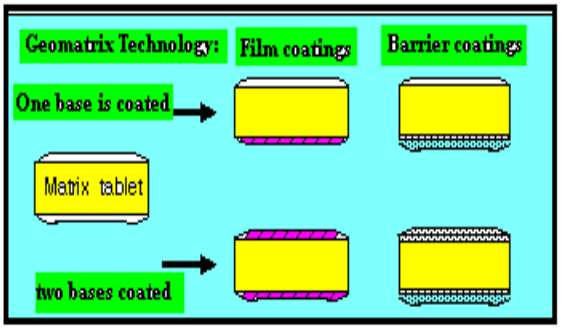
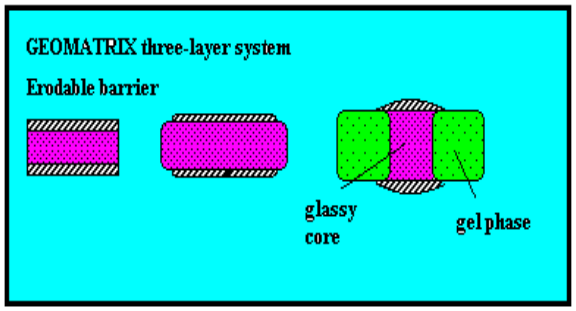
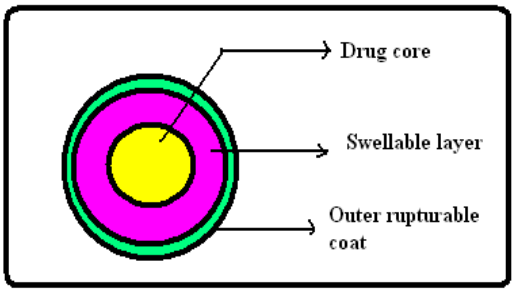


Figure 5:Delivery systems with rupturable coating layer and erodible coating layers





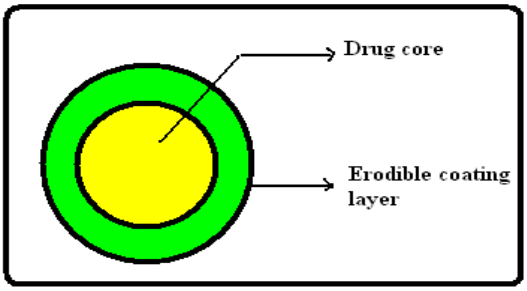


Figure 7: Schematic diagram of a one layer pulsatile DDS with an impermeable capsule body and pulsatile DDS with a two layer plug.

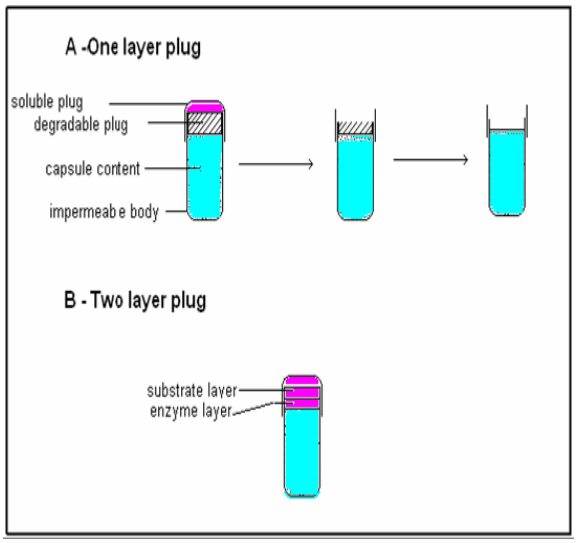
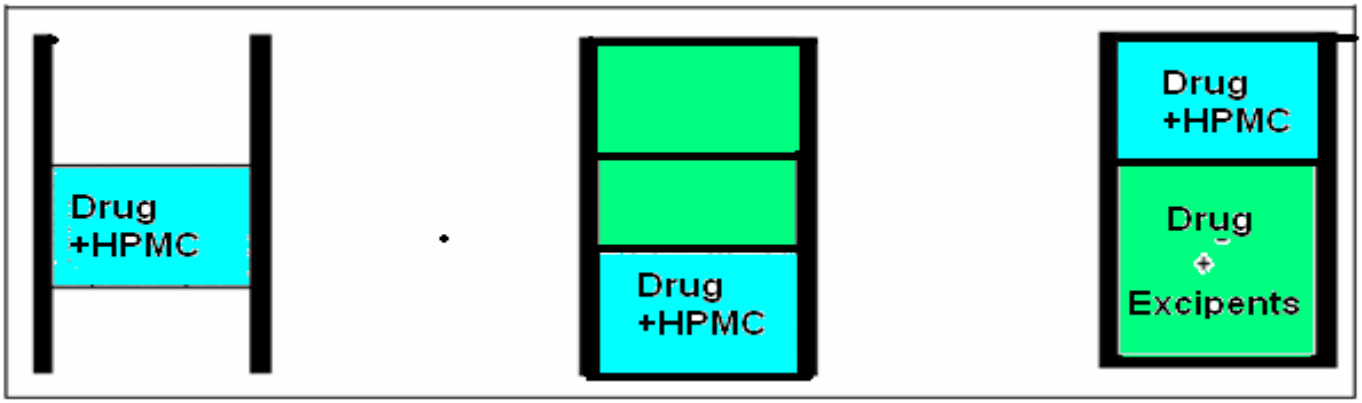


Figure 8: Configuration of multifunctional matrix delivery system.



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