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Switch to Modern Pulsatile Capsule Technology

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Multiarticulate drug delivery systems are especially useful for controlled or delayed release oral formulations to obtain different release patterns. Consequently, multiarticulate drug delivery systems provide tremendous opportunities for designing new controlled and delayed release oral formulations. Recently pulsatile delivery and multiarticulate dosage forms are gaining much favor over single-unit dosage forms in pharmaceutical applications. Recently pharmaceutical companies developed various technologies that fulfill unmet medical needs in the treatment of various diseases. Pulsatile drug delivery systems (PDDS) have attracted attraction because of their multiple benefits over conventional dosage forms. They deliver the drug at the right time, at the right site of action and in the right amount, which provides more benefit than conventional dosages and increased patient compliance.

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This review covers most important & acceptance marketed new developed technology Pulsincap™, Diffucaps®, CODAS®, OROS® and SODAS® technology disease where in PDDS are promising include asthma,pepticulcers,cardiovascular ailments,arthritisand attention deficit syndrome in children and hypercholesterolemia.Pulsatile drug delivery systems have the potential to bring new developments in the therapy of many diseases.

Key word: Pulsatile drug delivery, Degradable Polymer, Controlled releas.

1. Introduction:

In recent year considerable attention was been focused on the development of Pulsatile drug delivery system. Pulsatile drug delivery system shows most popular because it shows controlled release dosage form. Oral controlled drug delivery systems are generally used due to convenient dosage form & it also release the drug in constant or variable rates. In this system drug release generally occurs with specific window for prolonged period of time. There are certain conditions for which constant release pattern i.e. a zero-order release is not suitable and that demand release of a drug after a lag time. In other words, they require pulsatile drug delivery system. Pulsatile drug delivery is time and site-specific drug delivery, thus providing spatial and temporal delivery and increasing patient compliance. These systems are designed according to the circadian rhythm of the body. Capsule dosage form is more convenient for pulsatile dosage form because we can encapsulate different layer of polymer & layer for releasing the drug in different area.

Early 19th Century Mathews developed first capsule dosage form from gelatin. Since then this technology has been continuously improved & refined.There are many other conditions that demand pulsatile release, like many body functions that follow circadian rhythms, such as secretion of hormones [including follicle stimulating hormone (FSH), luteinizing hormone (LH), luteinizing hormone releasing hor-mone (LHRH), estrogen and progesterone], acid secretion in the stomach, gastric emptying and gastrointestinal blood trans fusion.[1-3]

2. Advantage of Pulsatile Capsule Drug delivery system:

I. Extended daytime or nighttime activity

II. Reduced side effects

III. Reduced dosage frequency

IV. Reduction in dose size

V. Improved patient compliance

VI. Lower daily cost to patient due to fewer dosage units are required by the patient in therapy.

VII. Drug adapts to suit circadian rhythms of body functions or diseases.

VIII. Drug targeting to specific site like colon.

IX. Protection of mucosa from irritating drugs.

X. Drug loss is prevented by extensive first pass metabolism.

XI. Patient comfort and compliance.[4]

Oral drug delivery is the most common and convenient for patients and a reduction in dosing frequency enhance compliance

There are different types of body conditions that demand for pulsatile drug delivery system:

a. Body function that follow cardiac rhythm

b. Secretion hormones & acidic stomach

c. Drugs that produce biological tolerance demand for a system that will prevent their continuous presence in the biphasic

d. The lag time essential for the drugs that undergo degradation in gastric acidic medium

e. Targeting drug on distal organ of gastro-intestinal track like the colon requires that the drug release is prevented in the upper two third portion of GIT

f. The drug undergoes first pass metabolism resulting reduce bioavailability altered steady state levels of drug and metabolites

3. Disadvantage of Pulsatile Capsule Drug delivery system:

- Low drug loading capacity and incomplete release of drug.
- Multiple manufacturing steps.

4. Categories of Pulsatile Drug Delivery system:

4.1 Time Controlled Pulsatile Capsule release technology:

In any release from a dosage form there is most important factor like erodible coating layer.

4.2 Bulk Eroding System:

Bulk erosion means that entry of water or heavy molecular chemical body fluid moves faster than rate of degradation of layer. Degradation takes place throughout the polymeric system up to reaching critical molecular weight. Base on time degradation of products become small enough to be solubilized, structure should be more porous.[5]

4.3 Surface Eroding System:

Surface erosion mediated release, the release of therapeutic from bulk degradation polymers is more complicated in addition to polymer degradation. Diffusion of therapeutic plays important role. Pigmented polymeric materials, including coatings and paints, undergo surface erosion. The mechanisms involved are complex because of the presence of degrading (polymer) and non-degrading (pigments and fillers) domains. It is further complicated by the shadowing effect of inorganic particles that prevent the degradation of the polymer and the catalytic influence of inorganic particles that accelerate degradation of the polymer. These mechanisms result in loss of

gloss, surface roughness, cracking, loss of mechanical properties, changes in color, etc. It is independent of the gastrointestinal motility, pH, enzyme and gastric residence.[6]

4.4 Delivery System with rupturable coating layer:

This system depends on disintegration of coating layer for release of the drug. The coating can be achieved by effervescent excipients, swelling agents. These Swelling agent produces osmotic pressure. An effervescent mixture of citric acid and sodium bicarbonate has been reported, wherein the mixture was incorporated in a tablet core coated with ethyl cellulose. The release may depend on mechanical property of the thickness of the coating layer. It is reported the weak & non flexible ethyl cellulose film ruptured compared with flexible films. Core containing drug is used as model drug which is prepared by direct compression of different ratios spray-dried lactose & micro crystalline cellulose & were then coated with inner swelling layer contain super disintegrate or other rupturable layer of cellulose.[6-10]

Bai et al. invented a pulsatile drug delivery system comprising a plurality of particles that were divided into several individual delivery units, each having its own distinct composition. The individual particles had the same composition as the internal core, but the thickness of the external coating layer varied. Drug delivery was controlled by the rupture of the membrane. The timing of release was controlled by the thickness of the coating and the amount of water-soluble polymer needed to achieve the pulsed release.[11]

4.6 Multiple Unit Pulsatile System:

More reliable gastric emptying patterns are observed for multiarticulate formulations as compared to single-unit formulations, which suffer from ‘all or none’ concept. As the units of multiarticulate systems are distributed freely throughout the gastrointestinal tract, their transport is affected to a lesser extent than single-unit formulations by the transit of food.[12]

5. Marketed Technologies of Pulsatile Drug Delivery system:

Different marketed technologies have been developed, they are comprised of

5.1 PulsinCap™ Technology:

It is an oral drug delivery technology that enables once daily pulsatile dosing. The transit properties of drug & hydrogel enhance the overall absorption-time window and offer improved bioavailability compared to tablet matrix forms. This device consists of non-disintegrating half capsule body sealed at the open end. The drug is given with hydrogel plug as pellet form that is covered by water soluble cap. Total unit is coated with enteric polymer to avoid the problem from gastric irritation or disturbance. [13,14]

Patel and Patel developed a modified Pulsincap device containing diclofenac sodium to target the drug in the colon. This is a site-specific and time-dependent formulation; i.e., by administering the formulation at bed time, symptoms that are experienced early in the morning are avoided. This therapeutic effect is prolonged by continuously releasing the medication over an extended period of time after administering a single dose. The objective of the study was to explore the time- and pH-dependent controlled drug delivery of Diclofenac Sodium using the pulsincap system.[15]

Working Style: At the time of contact with dissolution fluid, it swells after a lag time the plug pushes outside the capsule & release the drug. Some formulation shows form of bed or granule which has four-layer structure like core drug (Most inner layer),swelling agent (as Plug system), outer membrane (Water Insoluble polymer). The penetration of Gastrofluid through the outer membrane causes expansion of swelling agent. After swelling of swelling agent resulting of stress leads to destruction of the membrane rapid drug release. Polymers are used as per viscosity.

Different other approaches are enteric coated, time released, press coated tablets. In this enteric coated tablet first tablets are developed by pressing then enteric polymer is given for time release. Normally common polymer is used Hydroxypropyl cellulose or Hydroxy methyl cellulose. Normally various drug which are working on specific targeted zone like colon, Specific nerve stimulant or Pulmonary system etc. at time specific action by administration of drug. Advantage of the drug helps in single dose which working for prolonged time & maintain sustainable Ph.[16]

5.2 Diffitub Technology:

It is customizing release &region-specific delivery. It is mixing of blend of waxes and hydrophilic polymers that control the drug release through diffusion of matrix. It is practically useful for high dose products and high dose drug concentration. Drug is working through sustainable release in one dose /day. It is applicable for soluble & insoluble products. The drug is packed in polymeric matrix in totally tight sealing condition with semipermeable sealing condition.

5.3 Duocap Capsule Technology:

It can be used for immediate release or combined release—for example solubilized prebiotics in the outer capsule and probiotics in the inner capsule. The prebiotic releases immediately and the probiotic release later.

The inner capsule of this unique delivery system can contain liquid, semi-solids, powder or pellets, while the outer capsule can be either a liquid or semi-solid formulation.

The outer capsule typically is used for immediate release of a combination product or first phase of a dual release formulation. The liquid or semi-solid formulation of the outer capsule provides fast liquid release of the ingredient. Lipid-based formulations in either the inner and/or outer capsules may be developed to improve the bioavailability of the formulation.[17]

Capsugel has extensive experience in formulating combination products with incompatible compounds and with timed supplementation.

5.4 CODAS® Technology:

In certain cases, immediate release of drug is undesirable. A delay of drug action may be required for a variety of reasons. Chronotherapy is an example of when drug release may be programmed to occur after a prolonged interval following administration. Elan Drug Technology developed CODAS® technology to achieve this prolonged interval. The many advantages of the CODAS® technology include a delivery profile designed to compliment circadian pattern, controlled onset, an extended release delivery system, rate of release essentially independent of pH, posture and food, "sprinkle" dosing by opening the capsule and sprinkling the contents on food, reduction in effective daily dose and drug exposure, gastrointestinal tract targeting for local effect and reduced systemic exposure to achieve a target profile.[18,19]

5.4.1 Advantages:

(i) CODAS technology includes a delivery profile designed to complement circadian pattern, controlled onset, an extended release delivery system, rate of release essentially independent of pH, posture.

(ii)Food, "sprinkle" dosing by opening the capsule and sprinkling the contents on food, reduction in effective daily dose and drug exposure, gastrointestinal tract targeting for local effect and reduced systemic exposure to achieve a target profile.[20]

5.5 Geoclock Capsule Technology:

It is new oral drug delivery system. In this tablet has an active drug inside an outer layer consisting of mixture of hydrophobic wax and brittle material to obtain pH-independent lag time pH-independent lag time. Core drug delivery at predetermined layer. This dry coating is designed to

allow the time release of both slow release & immediate release active inner tablet first. Then gradually degraded surrounding outer shell disintegrates. It is also applicable in colonic drug delivery system at specific time throughout the layer. Lodotra™ has been designed maximum plasma level reached after 6hrs of intake. A patient swelled the tablet 10pm before going to sleep, with the dose of prednisone not being release until 2am & reaching maximum plasma at 4am, which is optimum timing to relive stiffness & pain of waking. It is also used in rheumatoid arthritis.[21]

5.6 OROS Capsule Technology:

Osmotic drug delivery uses the osmotic pressure of drug or other solute (Osmogenes) for controlled delivery of drug. The delivery rate of zero order is achievable with osmotic system. Delivery may be delayed, if desired. For oral osmotic system, drug release is independent of gastric Ph& hydrodynamic condition which is mainly attributed to the unique properties of semipermeable membrane in coating osmotic formulation. A high degree of in-vivo -in vitro correlation (IVIVC) obtained is osmotic system because the factors that are responsible for causing differences the release profile. Semipermeable membrane has sufficient wet strength & water permeability. Cellulose acetate is commonly employed semipermeable membrane for the preparation of osmotic pumps. In Osmotic Bursting osmotic pump core component is produced from API with osmogene, which is coated with semi permeable membrane without delivery orifice. When place in aqueous environment, water is imbibed by hydraulic pressure is build up inside the system, then wall ruptures & contents released. In Push Pull Osmotic Pump (PPOP) system they contain two or three

compartments separated by elastic diaphragm. Upper compartment contain drug with or without osmogene (Drug compartment nearly 60-80%) and lower compartment (Push Compartment) contain osmogene at 20-40%. It is bilayer tablet with semipermeable membrane. L-OROS® has two set of capsule Hard cap& soft cap. L-OROS® cap the drug layer and osmotic engine are encased in hard capsule which is surrounded by the rate controlling semipermeable membrane. A barrier layer composed of an inert substance separated drug layer from osmotic engines. A delivery orifice is laser drilled at the opposite end of the osmotic engine providing an outlet of drug. The liquid drug formulation is encased in soft capsule. It is turn surrounded by a barrier layer, osmotic engines & semipermeable membrane in order. A delivery orifice in drilled through semipermeable membrane, osmotic engine & barrier layer.[22-25]

5.7 Spheroidal oral drug absorption system (SODAS):

SODAS® (Spheroidal Oral Drug Absorption System) is Elan's Multiparticulate drug delivery system. Based on the production of controlled release beads, the SODAS® technology is characterized by its inherent flexibility, enabling the production of customized dosage forms that respond directly to individual drug candidate needs. Elan Corporation can provide a number of tailored 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. Alternatively, the opposite scenario can be achieved where drug release is delayed for a number of hours. An additional option is pulsatile release, where a once daily dosage form can resemble multiple daily doses by releasing drug in discrete bursts throughout the day.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.[26]

5.7.1 Benefits offered by the SODAS® technology include:

controlled absorption with resultant reduction in peak to trough ratios

targeted release of the drug to specific areas within the gastrointestinal tract

absorption independent of the feeding state suitability for use with one or more active drug candidate facility to produce combination dosage forms “sprinkle dosing” by administrating the capsule contents with soft food once or twice daily dose resembling multiple daily dose profiles

5.8 Cross-linked DNA capsules:

To prepare hollow microcapsule composed of native DNA, we developed a templating method using porous calcium carbonate microcapsule as sacrificial templates. At first DNA was absorbed onto calcium carbonate microparticle, then the absorbed DNA was covalently cross-linked with each other by using ethylene glycol. After the dissolution of the templates, the resultant DNA capsules ranged from 1.5-8μm in diameter, according to ionic strength. The low cross linked & high cross-linked DNA capsules exhibit enzymatic degradability and permeability that was dependent on molecular weight of macromolecular solute. This method is used for the preparation of various single components of Polymeric capsules.

6. Conclusion:

A lot of work is being done to achieve pulsatile release so that the drug release can be delivered according to cardiac rhythm of our body. Advancis Pharmaceutical Corp., German town, Maryland, USA has developed once-a-day pulsatile delivery system called Pulsys®. Which is enables delivery of different antibiotic in regular basis. The rationale behind designing such a system is that it has been reported that antibiotics are more effective against fast-growing bacteria. When an immediate release antibiotic is administered, bacteria respond to it by going into a dormant stage, while the administration of a pulsatile system in such a case is more effective because the regular release of

increased pulses of antibiotic does not let defense system of the bacteria to go into a dormant stage. Pulsatile delivery provides significant amount of therapeutic benefits, delivery of drug at right time, place, amount in patient's body. The etiology of the difficult diseases can be linked to the release of the specific drugs through these systems, which would definitely result in the betterment of the therapy. During the last two decades, pharmaceutical technology has grown leaps and bounds and, with the advent of pulsatile drug delivery, one can remain assured of accomplishment of goal for safe & effective therapy.

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