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Review Article

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Pulsincap Osmotically Driven Capsule Based On Push-Pull Technology: An Overview

Shaikh Siraj N*, G.J. Khan, Shaikh Mohsin F, Fakir Hina S, Shaoor Ahmad S, Shaikh Salman I.

Department of Pharmaceutics, Ali Allana college of Pharmacy, Akkalkuwa, Dist. Nandurbar (M.S.), India.

ABSTRACT

Pulsatile systems are offers a more of attraction because as they deliver the drug at the right amount, right site of action and at the right time, and providing target delivery of pharmaceuticals and increasing patient compliance and flexibility. These systems are formulated based on the body circadian rhythm. The basic principle for the use of pulsatile release is for the drugs where a zero-order release or a constant drug release, is not desired. The pulsatile effect on the release of drug as a “pulse”, and isto be designed in such a way that a complete and rapid drug release should follow the lag time. Many marketed products available in form of once-a-daily formulation based on pulsatile release like Push-pull osmotic Pulsincap is one of which include in pulsatile drug delivery which is described here.

Keywords: Pulsincap, Push-pull, Osmotic, Controlled, Lag time

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*Corresponding Author

Prof. Shaikh Siraj N
HOD, Department of Pharmaceutics,
Ali Allana college of Pharmacy,
Akkalkuwa, Nandurbar, M.S, India.
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1. Introduction

Conventional drug delivery systems have somewhat control over drug release and almost no control over effective concentration at the site of action. Like dosing pattern may be result in constantly alternating, unpredictable or undesirable plasma concentrations. This results in the development of various controlled drug delivery system. Among which the

Pulsatile drug delivery systems (PDDS)/ osmotic drug delivery system (ODDS) are gaining importance as these systems deliver the drug at specific time as per the path physiological need of the disease, resulting in improved patient therapeutic efficacy and compliance. Push-pull osmotic tablets can also be used for the delivery of drugs,

which are poorly water-soluble and water soluble at a constant rate. Over other techniques to improve the bioavailability of these drugs formulation of osmotic drug delivery system is the most suitable one. Osmotic drug delivery systems release the drug with the zero order kinetics. Drugs can be delivered in a controlled way over an extended period of time by their constant release. The dosage forms include for oral and other systems. For 90% of drugs, oral route is the most compatible route of administration. Many molecules may under BCS II & I class this is the limitation of it. Development of a longer release dosage form also wants something absorption through gastro-intestinal tract (GIT) [1].

Various modified release drug products:

1. **Extended Release:** It leads to two fold lesser the dosing frequency as compared to immediate release dosage forms.
2. **Controlled release:** It works slow drug release over extended period of time but not at predetermined rate.
3. **Sustained release:** It delivers drug at predetermined rate over an extended period of time.
4. **Delayed Release:** It releases discrete portion of drug at a time other than just after administration, although one portion may be released slowly after administration.
5. **Targeted Release:** It deliver drug at or near the desire site of action and may have extended release properties.
6. **Repeated Action:** It is designed to release first dose at start, followed by second dose of drug at a last.
7. **Prolonged Action:** It releases drug promptly and give continuous supply of drug over an extended period of time [2].

Pulsatile DD System:

Pulsatile release dosage forms release drug in pulsatile manner and maintain plasma drug level within therapeutic range. Pulsatile system is amongst one of them and gaining a lot of interest as it is increasing patient compliance by means of providing time- and site-specific drug delivery system, thus providing special and temporal delivery. Pulsed or pulsatile drug release is defined as the rapid and transient release of a certain amount of drug molecules within a short time-period immediately after a predetermined off-release period [3]. "Chronopharmaceutics" consists of two words chronobiology and pharmaceutics. Chronobiology is the study of biological rhythms and their mechanisms. There are three types of mechanical rhythms in our body.

They are:

1. **Ultradian:** Oscillation of shorter duration is termed as ultradian (more than 1 cycle per 24 h)
2. **Infradian:** Oscillations that is longer than 24 h (less than one cycle per day).
3. **Circadian:** "Circa" means about and "dies" means day. Circadian rhythm regulates many body functions in humans, viz., metabolism, behaviour, Physiology, sleep patterns, hormone production, etc. In case of cardiovascular diseases, BP is at its lowest during the sleep cycle and rises steeply during the early morning period. Platelet aggregability is increased and fibrinolytic activity is decreased in the morning, leading to a state of relative hypercoagulability of

the blood. Circadian increase in the blood sugar level after meal has been observed in Diabetes mellitus [3].

Historical Background:

In 1729, the first known experiment on biological rhythms was conducted by French astronomer Jean Jacques d'Ortous de Mairan. Biological rhythms not only impact the function of physiology, but the pathophysiology of diseases. If symptoms of a disease became worse during the night or in the early morning the timing of drug administration and nature of the drug delivery system need careful consideration. For example, in an asthmatic patient circadian changes are seen in normal lung function, and in cardiovascular diseases, several functions (e.g. Blood pressure, heart rate, stroke volume, cardiac output, blood flow) of the cardiovascular system are subject to circadian rhythms where pulsatile drug delivery system can be useful. About 75 years after discovery of the osmosis principle, it was first used in the design of drug delivery systems [6]. Rose and Nelson, the Australian scientists, were initiators of osmotic drug delivery [4].

In 1955, they developed an implantable pump, which consisted of three chambers: a drug chamber, a salt chamber contains excess solid salt, and a water chamber. The drug and water chambers are separated by rigid semi-permeable membrane. The difference in osmotic pressure across the membrane moves water from the water chamber into the salt chamber. The volume of the salt chamber increases because of this water flow, which distends the latex diaphragm separating the salt and drug chambers, thereby pumping drug out of the device. The design and mechanism of this pump is comparable to modern push-pull osmotic pump. The major disadvantage of this pump was the water chamber, which must be charged before use of the pump. The pumping rate of this push-pull pump is given by the equation.

$$dM/dt = dV/dt \times c$$

In general, this equation, with or without some modifications, applies to all other type of osmotic systems.⁴

2. Classification of Pulsatile Drug Delivery Systems:

I. Time controlled pulsatile drug delivery

(A) Single unit pulsatile systems

(1) Capsule based systems

Pulsincap system

(2) Capsular system based on Osmosis

(a) 'PORT' System

(b) System based on expandable orifice

(c) Delivery by series of stops

(d) Pulsatile delivery by solubility modulation

(3) Pulsatile system with erodible or soluble barrier coatings

(a) The chronotropic system

(b) 'TIME CLOCK' System

(c) Compressed tablets

(d) Multilayered Tablets

(4) Pulsatile system with rupturable coating

(B) Multi-particulate / Multiple unit systems

(1) Pulsatile system with rupturable coating

Time –controlled Explosion system (TCES)

(2) Osmotic based rupturable coating system

(3) Pulsatile Delivery by Change in Membrane Permeability

Sigmoidal Release System**II. Stimuli induced pulsatile systems**

- (1) Temperature induced systems
- (2) Chemical stimuli induced pulsatile systems
 - (a) Glucose-responsive insulin release devices
 - (b) Inflammation induced pulsatile release device
 - (c) Drug release from intelligent gels responding to antibody concentration
 - (d) pH sensitive drug delivery system

III. Externally regulated pulsatile drug delivery [3]**Pulsincap:**

Pulsincap was firstly developed by R.R. Scherer International Corporation (Michigan US). This is osmotically driven push pull technology firstly pull the dissolution fluid by osmotically and the plug is swells and pushed itself outside the capsule and rapidly released the drug. The device consists of a water-insoluble half capsule body sealed at the open end with a hydro-gel plug that is covered by a water-soluble cap. The whole body unit is coated with polymer to avoid the gastric problem. The capsules come in contact with the dissolution fluid, it swells, and after a lag time, the plug pushes itself outside the capsule cap and rapidly releases the drug [4]. There are another two approaches, one is generation of hydrostatic pressure by using biodegradable capsules of poly (lactic acid) (PLA) containing the drug along with sodium bicarbonate/citric acid and glucose were prepared. Thin poly (lactic-co-glycolic acid) (PLGA) membrane was utilized on one end for allowing water penetration inside the capsules. Water penetrates into the capsule through the thin poly (lactic-co-glycolic acid) (PLGA) membrane side, which generates effervescence due to reaction caused between the citric acid and sodium bicarbonate, generating carbon dioxide gas [5].

Another approach is Pulsincap for position controlled pulsatile release which is achieved by using coating membranes. One of the coating membranes is composed of an enteric polymer and the second membrane barrier is composed of a mixture of water-insoluble polymer and an enteric polymer. The composition and the thickness of the polymeric membranes determine the lag time and the duration of the drug release from each of the bead populations [6]. In other preparations, various organic acids such as citric acid, fumaric acid, succinic acid, tartaric acid or malic acid, is included and a maleic acid filled membrane may be provided between the first and second membrane layers to provide for the time-separated pulses. The acids in between the membranes may delay the dissolution of the enteric polymer in the inner layer, thereby increasing the lag time as well as decreasing the rate of release of the active ingredient from the coated micro particulates. The enteric coating membrane is generally incorporated in the innermost layer to have the drug released in the lower intestine.

This is a site-specific and time-dependent formulation; i.e., by administering the formulation at bedtime, 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 [6].

Basic Concept:**Osmosis:**

Diffusion of fluid through a semipermeable membrane from a solution with a low solute concentration to a solution with a higher solute concentration until there is an equal solute concentration on both sides of the membrane.

Osmotic Pressure:

Osmotic pressure is the force caused by a solution passing through a semi permeable surface by osmosis, which is equal to the force required to resist the solution from passing back through the surface.

Principle of Osmosis:

The first report of an osmotic effect dates to Abbenollet {1748}. But Pfeffer obtained the first quantitative measurement in 1877. In Pfeffer experiment a membrane permeable to water but impermeable to sugar is used to separate a sugar solution from pure water. A flow of water then takes place into the sugar solution that cannot be halted until a pressure is applied to the sugar solution. Pfeffer showed that this pressure, the osmotic pressure of the sugar solution is directly proportional to the solution concentration and the absolute temperature. Within few years, Vant Hoff had shown the analogy between these results and ideal gas laws by the expression

$$= \pi c RT$$

Where, π = Osmotic pressure, ϕ = osmotic coefficient, c = molar concentration, R = gas constant

T = Absolute temperature.

Osmotic pressure is a colligative property, which depends on concentration of solute that contributes to osmotic pressure. Solutions of different concentrations having the same solute and solvent system exhibit an osmotic pressure proportional to their concentrations. Thus a constant osmotic pressure, and thereby a constant influx of water can be achieved by an osmotic delivery system that results in a constant zero order release rate of drug. Osmotic pressures for concentrated solution of soluble solutes commonly used in controlled release formulation are extremely high ranging from 30 atm for sodium phosphate up to 500atm for a lactose-fructose mixture, as their osmotic pressure can produce high water flow across semi permeable membrane. The osmotic water flow through a membrane is given by the equation

$$dv/dt = A Q \quad \Delta \pi / L$$

Where,

dv/dt = water flow across the membrane of area A in cm^2 ,

L = thickness, Q = permeability and

$\Delta \pi$ = the osmotic pressure difference between the two solutions on either side of the membrane.

This equation is strictly for completely perm selective membrane that is membrane permeable to water but completely impermeable to osmotic agent [4,7].

Basic components:**Suitable Drug candidate:**

Drug which have short biological half-life and which is used for prolonged treatment are ideal candidate for this systems. Various drug candidates such as Diltiazem HCl, Carbamazepine, Metoprolol, Oxprenolol, Nifedipine, Glipizide, Valsartan, Atorvastatin, etc are formulated by this way [4,8].

Basic Criterion for Drug Selection:

- Short biological Half-life (2- 6 hrs)
- High potency
- Required for prolonged treatment

Empty capsules:

The '0' sized hard gelatin capsules are used. These capsules separated by their caps and bodies and the caps are remain as a water soluble but the bodies were treated by two method to insolubilize in water [4].

- Dip coating by rate retarding polymers
- Formaldehyde vapours treatment.

Semi Permeable Membrane:

A fundamental part of the osmotic drug delivery system is the semi-permeable membrane housing. Therefore, the polymeric membrane selection is key to the osmotic delivery formulation. Generally, in osmotic pumps, the semi-permeable must be 200-300 μm thick to withstand the pressure within the device. The various coating polymers are used for the semi-permeable coating are cellulose acetate, cellulose acetate butyrate, cellulose triacetate and ethyl cellulose and Eudragits [4].

Ideal Property of Semi Permeable Membrane:

The Semi Permeable Membrane must meet some performance criteria

- The material must possess sufficient wet strength (-105) and wet modulus so as to retain its dimensional integrity during the operational lifetime of the device.
- The membrane exhibit sufficient water permeability so as to retain water flux rate in the desired range. The water vapor transmission rates can be used to estimate water flux rates
- The reflection coefficient and leakiness of the osmotic agent should approach the limiting value of unity. Unfortunately, polymer membranes that are more permeable to water are also, in general more permeable to the osmotic agent.
- The membrane should also be biocompatible

Coating solvents:

The primary functions of solvent system are to dissolve or dispersed the polymer and other additive and convey them to substrate surface. solvent used to prepare polymeric solution include inert inorganic and organic solvents that do not adversely harm the core, wall and other material. the various types of solvents and their combinations are as follows: Methylene chloride, methanol, isopropyl alcohol, dichloromethane, ethyl acetate, acetone, carbon tetrachloride, cyclohexane, butyl alcohol, water etc and the mixture of solvents such as acetone-methanol (80:20), methylene chloride- methanol (79:21), acetone-ethanol(80:20), methylene chloride-methanol-water (75:22:3) [4,9].

The ideal solvent system should have following properties.

- It should easily and completely dissolve the polymer. It should easily disperse other coating components into solvent system.
- It should not give extremely viscous solution with Small concentration of polymer (2-10%) because it create process problem.
- It should be odorless, colorless, tasteless, inexpensive, nontoxic and non-irritant.

- It should have rapid drying rate.

Plasticizers:

Different types and amount of plasticizers used in coating membrane also have a significant importance in the formulation of osmotic systems. They can change visco-elastic behavior of polymers and these changes may affect the permeability of the polymeric films. Some of the plasticizers used for Eg. Polyethylene glycols, Ethylene glycol monoacetate, and diacetate- for low permeability, Tri ethyl citrate and Diethyl tartarate or Diacetin- for more permeable films [4].

Pore forming agent:

These agents are particularly used in the pumps developed for poorly water soluble drug and in the development of controlled porosity or multiparticulate osmotic pumps. These performing agents cause the formation of microporous membrane. The microporous wall may be formed in situ by a pore-former by its leaching during the operation of the system. The pore formers can be inorganic or organic and solid or liquid in nature. For example, alkaline metal salts such as sodium chloride, sodium bromide, potassium chloride, potassium sulphate, potassium phosphate etc., alkaline earth metals such as calcium chloride and calcium nitrate, carbohydrates such as sucrose, glucose, fructose, mannose, lactose, sorbitol, and mannitol, diols and polyols such as poly hyric alcohols and polyvinyl pyrrolidone can be used as pore forming agents [4].

Osmotic agents:

These are also known as osmogens or osmogents and are used to create osmotic pressure inside the system. Osmotic agents maintain a concentration gradient across the membrane. They also generate a driving force for the uptake of water and assist in maintaining drug uniformity in the hydrated formulation. Upon penetration of biological fluid into the osmotic pump through semipermeable membrane, osmogens are dissolved in the biological fluid, which creates osmotic pressure buildup inside the pump and pushes medicament outside the pump through delivery orifice. Osmotic components usually are ionic compounds consisting of either inorganic salts or hydrophilic polymers. Osmotic agents can be any salt such as sodium chloride, potassium chloride, sulfates of sodium, potassium and lithium. Additionally, sugars such as glucose, sorbitol, mannitol, sucrose, dextrose, fructose and inorganic salts of carbohydrates can act as osmotic agents [10].

Flux regulators:

Delivery systems can be designed to regulate the permeability of the fluid by incorporating flux regulating agents in the layer. Hydrophilic substances such as polyethethylene glycols (300 to 6000 Da), polyhydric alcohols, polyalkylene glycols, and the like improve the flux, whereas hydrophobic materials such as phthalates substituted with an alkyl or alkoxy (e.g., diethyl phthalate or dimethoxy ethylphthalate) tend to decrease the flux. Insoluble salts or insoluble oxides, which are substantially water impermeable materials, also can be used for this purpose [4].

Wicking agent:

A wicking agent is defined as a material with the ability to draw water into the porous network of a delivery device. A wicking agent is of either swellable or non-swellable nature.

They are characterized by having the ability to undergo physisorption with water. Physisorption is a form of absorption in which the solvent molecules can loosely adhere to surfaces of the wicking agent via Vander Waals interactions between the surface of the wicking agent and the adsorbed molecule. The function of the wicking agent is to carry water to surfaces inside the core of the tablet, thereby creating channels or a network of increased surface area. Materials, which suitably for act as wicking agents include colloidal silicon dioxide, kaolin, titanium dioxide, alumina, niacinamide, sodium lauryl sulphate (SLS), low molecular weight poly vinyl pyrrolidone (PVP), m-pyrol, bentonite, magnesium aluminum silicate, polyester and polyethylene [4].

Hydrophilic and Hydrophobic Polymers:

These polymers are used in the formulation development of osmotic systems for making drug containing matrix core. The selection is based on the solubility of the drug as well as the amount and rate of drug to be released from the pump.

The polymers are of either swellable or non-swellable nature. Mostly, swellable polymers are used for the pumps containing moderately water-soluble drugs, since they increase the hydrostatic pressure inside the pump due to their swelling nature. The non-swellable polymers are used in case of highly water-soluble drugs. Ionic hydrogels such as sodium carboxymethyl cellulose are preferably used because of their osmogenic nature.

Example: Hydroxyl ethylcellulose, carboxy methylcellulose, hydroxyl propyl methylcellulose, high molecular weight poly (vinyl pyrrolidone), Ethyl cellulose and wax materials.

Factor affecting on Pulsincap:

Drug Solubility:

For the osmotic system, solubility of drug is one of the most important parameters affecting drug release kinetics from osmotic pumps. The kinetics of osmotic drug release is directly related to the drug solubility within the drug core.

$$F(z) = 1 - S/ (1)$$

Where,

F(z) is the fraction released by zero-order kinetics, S is the drug's solubility (g/cm³), and ρ is the density (g/cm³) of the core tablet. Drugs with a density of unity and the solubility of

0.05 g/cm³ would be released with 95% zero-order kinetics, according to Eq. (1). At the same time, highly water-soluble drugs would demonstrate a high release rate that would be zero-order for a small percentage of the initial drug load. Thus, the intrinsic water solubility of many drugs might prohibit them from incorporation into an osmotic pump. Candidate drugs for osmotic delivery have water solubility in the range 50–300 mg/ml. Some of the approaches that have been used to modulate drug solubility within the core include Co-compression of the drug with excipients, which modulate the drug's solubility within the core;

- Use of effervescent mixtures to speed up the release of poorly soluble drug from the orifice;
- Use of various cyclodextrin derivatives to solubilize poorly water soluble drug;
- Use of alternative salt form that has optimum water solubility;
- Use of encapsulated excipient;

- Use of lyotropic crystals;
- Use of wicking agents.

Delivery orifice:

Majority of osmotic delivery systems contain at least one delivery orifice (preformed or formed in situ) in the membrane for drug release. Size of delivery orifice must be optimized to control the drug release from osmotic system. The size of the delivery orifice must be smaller than a maximum size S_{max} to minimize drug delivery by diffusion through the orifice. Furthermore, the area must be sufficiently large, above a minimum size S_{min}, to minimize hydrostatic pressure buildup in the system. Otherwise, the hydrostatic pressure can destroy the membrane and affect the zero-order delivery rate. Therefore, the cross-sectional area of the orifice should be maintained between the minimum and maximum values [8].

Osmotic pressure:

The first thing is to maintain osmotic pressure gradient between inside the compartment and the external environment. The release rate of a drug from an osmotic system is directly proportional to the osmotic pressure of the core proportional to the osmotic pressure of the core. The simplest and most predictable way to achieve a constant osmotic pressure is to maintain a saturated solution of osmotic agent in the compartment. If a saturated solution of the drug does not possess sufficient osmotic pressure, an additional osmotic agent must be added to the core formulation. The addition of carbonate or bicarbonate salt to the drug chamber offers an advantage since the effervescent action prevents the precipitated drug from blocking the delivery orifice in the tablet [10]. Polymeric osmogents are mainly used in the fabrication of PPOPs and other modified devices for controlled release of drugs with poor water solubility. These are swellable, hydrophilic polymers that interact with the aqueous fluids and swell or expand to an equilibrium state.

Semipermeable membrane:

Some of the membrane variables that are important in the design of oral osmotic system are:

Type and nature of polymer:

Any polymer permeable to water but impermeable to solute can be selected.

Membrane thickness:

Thickness of the membrane has a marked effect on the drug release from osmotic system, which is inversely proportional to each other.

Type and amount of plasticizer:

In pharmaceutical coatings, plasticizers or low molecular weight diluents are add into it to modify the physical properties and improve film-forming characteristics of polymers. Plasticizers can change viscoelastic behavior of polymers significantly. In particular, plasticizers can turn a hard and brittle polymer into a softer, more pliable material, and possibly make it more resistant to mechanical stress. These changes also affect the permeability of polymer films.

Evaluation of Oral Osmotic Drug Delivery Systems:

Oral osmotic drug delivery systems can be evaluated for following:

Visual inspection: To check smoothness, uniformity of coating, edge coverage and luster.

Coating uniformity: The uniformity of coating among the capsules can be estimate by determining the weight, thickness and diameter of the capsule before and after the coating.

Coat weight and thickness: The coat weight and thickness can be determine from depleted devices following careful washing and drying of the film, using standard analytical balance and screw gauge, respectively.

Orifice diameter:

The mean orifice diameter of Pulsincap can be determine microscopically using pre calibrated ocular micrometer.

Effect of pH: An osmotically controlled release system delivers its contents independently of external variables. To check this, dissolution media with different pH is used.

Effect of agitation intensity:

In order to study the effect of agitation intensity of the release media, release studies is carried out in dissolution apparatus at various rotational speeds.

In-vitro drug release:The *in-vitro* release of drug from the Pulsincap is done by using USP Dissolution apparatus Type I. The dissolution medium is 900 mL simulated intestinal fluid without enzymes. Temperature is maintained at $37 \pm 0.5^\circ\text{C}$ and rotation speed is adjusted to 50 RPM. The capsules are place in basket to ensure that they are remains at the bottom of the vessels. Exact 5 mL aliquots are withdrawn at hourly interval up to 15 h. The medium is replaced with 5 mL of fresh medium each time. Samples are analyse by UV spectrophotometer at respective nm.



Figure 1

Table 1: Marketed products

Product name	Chemical name	Type of delivery	Developer / Marketer
Glucotrol XL	Glipizide	Push-Pull	Pfizer
MinipressXL	Prazosin	Push-Pull	Alza
ProcardiaXL	Nifedipine	Push-Pull	Pfizer
Volmax	Albuterol	Push-Pull	MuroPharma
Alpress LP	Prazosin	Push-Pull	Pfizer
Concerta	Methyl phenidate	Push-Pull	Alza
Ditropan XL	Oxybutinin chloride	Push-Pull	UCB Pharma
CalanSR	Verapamil	Push-Pull	Alza

3. Conclusion

Pulsatile drug delivery is one such system that, by delivering drug at the right time, right place & in right amounts, holds good promises of benefit to the patients suffering from chronic problems like arthritis, asthma, hypertension, etc. Thus, designing of proper pulsatile drug delivery will enhance the patient compliance, optimum drug delivery to the target side & minimizing the undesired effects. Circadian rhythm of the body is an important concept for understanding the optimum need of drug in the body. The overall object of present review article is to aware the researchers and scholars regarding this recent approach of osmotically active drug delivery system based on the concept of bilayer (push-pull) osmotic Pulsincap technology [11].

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