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OSMOTIC PUMP DELIVERY SYSTEM : An Overview

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Abstract

Osmotic pumps are one of the systems for controlled drug delivery. Osmotic pressure, a colligative property, depends on the concentration of solute (neutral molecule or ionic species) that contributes to the 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 release rate of drug. Therefore, zero-order release, which is important for a controlled release delivery system when indicated, is possible to achieve using these platforms. In 1974, Theeuwes and Higuchi applied the principle of osmotic pressure to a new generation of controlled drug delivery devices with many advantages over other existing controlled drug delivery systems. The first of these devices, the elementary osmotic pump, is considered a typical delivery system that operates on osmotic principles. The number of marketed oral osmotically driven systems (OODS) has doubled in the last 10 years. General guidance on technology selection is described in light of the recent advances in the field. The clinical performance of these technologies is also discussed, with a focus on food effects and the in vivo-in vitro correlation. Special attention is paid to safety given the controversial case study of Osmosis. Overall, oral osmotically driven systems appear to be a promising technology for product life-cycle strategies.

Key Words: Osmotic pressure, osmotic agent, semi permeable membrane, Push-pull osmotic pump, Ensotrol Technology.

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Introduction

Osmotic systems technology potentially could be suitable for therapies in drug addiction. A once-daily system offering controlled drug delivery would maintain the therapeutic effect throughout the dosing interval by producing a steady plasma concentration level for 24 hours. The technology allows more than one drug in a delivery system; for example, a small amount of naloxone could be mixed with an orally administered narcotic agent. Not only would this permit continued daily therapy with the narcotic, but it also would limit the diversion potential of any take- home medication. The rate and extent of drug absorption from conventional formulations may vary greatly depending on the factors such as physico-chemical properties of the drug, presence of excipients, physiological factors such as presence or absence of food, pH of the gastro-intestinal tract (GIT) and so on.

Osmotic Pump Controlled Release Preparation is a novel drug delivery system with eternally drug delivery rate as characteristic. The osmotic-controlled release oral delivery system (OROS) is an advanced controlled release oral drug delivery system in the form of a rigid tablet with a semi-permeable outer membrane and one or more small laser drilled holes in it. As the tablet passes through the body, water is absorbed through the semipermeable membrane via osmosis, and the resulting osmotic pressure is used to push the active drug through the laser drilled opening(s) in the tablet and into the gastrointestinal tract. OROS is a trademarked name owned by ALZA Corporation, which pioneered the use of osmotic pumps for oral drug delivery.

Historical background

The first two products indomethacin, Osmosin and phenylpropanolamine, Acutrim TM, were launched in the 1980s. Osmosin (EOP) of Merk's had to be withdrawn from the market due to severe side effects such as GI irritation and perforation of the intestinal wall [Donnelly P.1980]. The controlled-porosity osmotic pump tablet concept was developed as an oral drug delivery system by Zentner et al (1985, 1991), Zentner and Rork (1990), Appel and Zentner (1991), and Mc Celland et al. (1991). Osmotically oral drug delivery system (OODS) development continued with two new OODS designs, the controlled-porosity osmotic pumps (CPOP) and the push–pull osmotic pumps (PPOP). The first CPOP was designed to decrease the risk of extremely localised drug-induced irritation at the site close to the orifice, as seen in the case of Osmosin. The applicability of the OODS to poorly soluble drugs was targeted by using PPOP. Thus, nifedipine PPOP (Procardia XL) was one of the most successful drug delivery systems of the last century, marking the revival of the OODS[1].

Merits of Osmotic drug delivery system

Osmotic drug delivery system for oral use offer distinct and practical advantage over other means of delivery. The following advantages contributed to the popularity of osmotic drug delivery system.

1. They typically give a zero order release profile after an initial lag.
2. The release mechanisms are independent on drug concentration.
3. Sustained and consistent blood levels within the therapeutic window.
4. Reduced side effects.
5. Deliveries may be delayed or pulsed if desired.
6. Drug release is independent of gastric pH and hydrodynamic condition.
7. They are well characterized and understood.
8. Delivery rate is independent of agitation outside, including GI motility.
9. Enhanced bioavailability of drug.

10.Reduced interpatient variability .
11.Release rate of drug is highly predictable and programmable.
12.Decrease dosing frequency.
13.Improved patient compliance.
14.Increased safety margin of high potency drugs.
15.Drug release from the OCODDSs exhibits significant in vitro-in vivo correlation within specific limits.
16.It is possible to attain better release rates than those obtained with conventional diffusion based drug delivery systems[2].

Demerits

1. High Cost.
2. If the coating process is not well controlled there is a risk of film defects, which results in dose dumping.
3. Hole Size is critical in case of elemetry osmotic system.
4. Drug release from the osmotic systems is affected to some extent by the presence of food.
5. Retrieval of therapy is not possible in the case of unexpected adverse event.
6. Rapid development of tolerance.
7. It may cause irritation or ulcer due to release of saturated solution of drug[3].

Osmosis

Osmotic systems utilize the principle of osmotic pressure for the delivery of drugs. The overall idea of osmosis came up by early cultures, when they realized that salt could be used to desiccate foods for long-term preservation. They observed that in saline environments, most bacteria, fungi, and other potentially pathogenic organisms become dehydrated and die or become temporarily inactivated because of osmosis only.

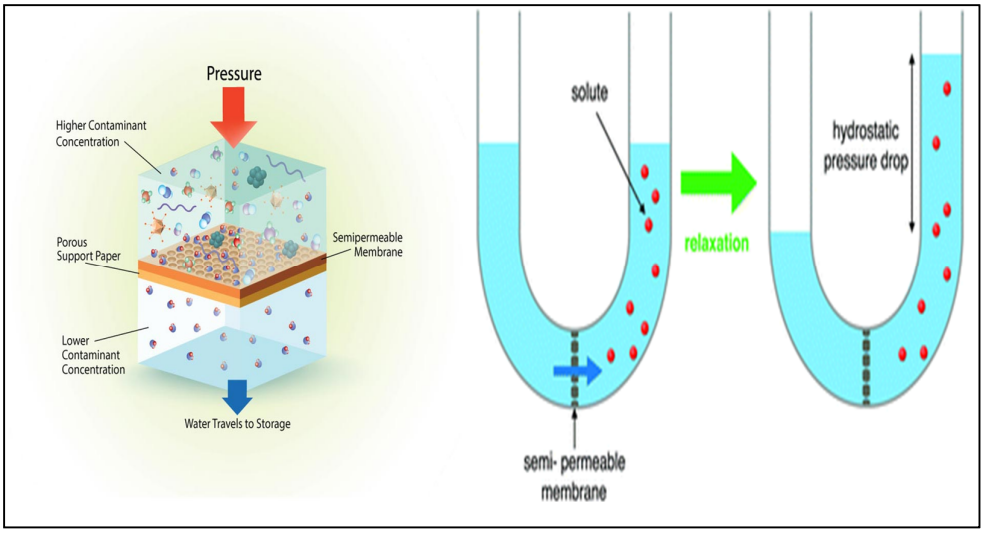


Fig.1: Process of Osmotic Pressure

Previously, natural materials were used by early researchers to study the mechanism of osmosis, but from the1960s, synthetic material came into the picture .Special attention has been given to osmosis through synthetic materials.

Principle

Osmosis can be defined as the spontaneous movement of a solvent from a solution of lower solute concentration to a solution of higher solute concentration through an ideal semipermeable membrane, which is permeable only to the solvent but impermeable to the solute. The pressure applied to the higher-concentration side to inhibit solvent flow is called the osmotic pressure[4].

The first osmotic effect was reported by Abbe Nollet in 1748. Later in 1877, Pfeffer performed an experiment using semi-permeable membrane to separate sugar solution from pure water. He showed that the osmotic pressure of the sugar solution is directly proportional to the solution concentration and the absolute temperature.

In 1886, Vant Hoff identified an underlying proportionality between osmotic pressure, concentration and temperature. He revealed that osmotic pressure is proportional to concentration and temperature and the relationship can be described by following equation.

$V\Pi = nRT$ …(1)

$\Pi = (n/V)RT$ …(2)

$\Pi = c\,RT$ ...(3)

Where, V = volume of the solution in liters , Π = osmotic pressure in atmospheres , n = number of moles of solute, c = molar concentration, R = gas constant ,equal to 0.082 L·atm/mol·K , T = Absolute temperature in K.

The preceding equation can be applied satisfactorily to describe the osmotic pressure of dilute solutions of nonelectrolytes such as sucrose and urea.Van't Hoff later observed that the osmotic pressure of electrolyte solutions were two, three, or more times greater than predicted by the general equation. Therefore, a factor i was introduced to account for the behavior of ionic solutions. The corrected equation for electrolyte solutions is written as follows:

$\pi = icRT$ ...(4)

By application of this equation, it is possible to calculate osmotic pressures for ionic solutions. Van't Hoff also observed thati approaches the number of ions as the molecule dissociates in an increasingly dilute solution. Moreover, the deviations of concentrated electrolyte solutions from ideal behaviour can be obtained from Raoult's law.

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.

Release Kinetics inelementary Osmotic Pumps

The elementary osmotic delivery system consists of an osmotic core containing drug and, as necessary, an osmogen surrounded by a semipermeable membrane with an aperture. A system with constant internal volume delivers a volume of saturated solution equal to the volume of solvent uptake in any given time interval. Excess solids present inside a system ensure a constant delivery rate of solute. The rate of delivery generally follows zero-order kinetics and declines after the solute concentration falls below saturation. The solute delivery rate from the system is controlled by solvent influx through the semipermeable membrane.The osmotic flow

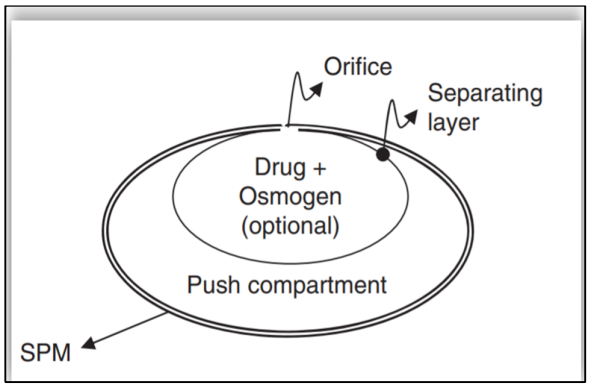


Fig.2: Scheme of OROS push-pull osmotic pump

of the liquid depends on the osmotic and hydrostatic pressure differences across the semipermeable membrane of the system.This phenomenon is the basic feature of nonequilibrium thermodynamics, which describes the volume flux $\frac{dV}{dt}$, across the semipermeable membrane in the form of the following equation :

$$\frac{dV}{dt} = \left(\frac{A}{h}\right) L_P(\sigma\Delta\pi - \Delta P) \quad \ldots(1)$$

where Δπ and ΔP = osmotic and hydrostatic pressure differences,respectively, across the membrane,L_P = mechanical permeability,σ = reflection coefficient, which accounts for leakage of solute through the membrane,A = surface area of the membrane,h = membrane thickness

The corresponding solute delivery rate dm/dt can be expressed as follows: $\frac{dm}{dt} = \left(\frac{A}{h}\right) L_P(\sigma\Delta\pi - \Delta P)C$ …(2)

where C is the solute concentration in the delivered fluid.As size (diameter) of the delivery orifice increases, the hydrostatic pressure of the system decreases, and (Δπ − ΔP) approximates Δπ. The osmotic pressure of the formulation π can be substituted for Δπ when the environmental osmotic pressure is small. Thus the equation can be simplified as follows: $\frac{dm}{dt} = \left(\frac{A}{h}\right)(L_P\sigma\pi)C$ ……..(3)

A constant k may replace the product L_Pσ, so the preceding equation further reduces to $\frac{dm}{dt} = \left(\frac{A}{h}\right) k\pi C$ …..(4)

The zero-order release rate of the elementary osmotic pump from t = 0 to time t_x, when all the solids dissolve and the solute concentration begins to fall below saturation, can be defined as follows: $\frac{dm}{dt} = \left(\frac{A}{h}\right) k\pi_S S$ ……..(5)

where S is the solubility at saturation, and π_S is the osmotic pressure at saturation. When the rate of dissolution is not limiting relative to the delivery rate through the aperture, the concentration C can be replaced with solubility S.

Key parameters that influence he drug design

Orifice size

To achieve an optimal zero-order delivery profile, the cross-sectional area of the orifice must be smaller than a maximum size S_{max} to minimize drug delivery by diffusion through the orifice. Further more, the area must be sufficiently large, above a minimum size S_{min}, to minimize hydrostatic pressure build up in the system. Otherwise, the hydrostatic pressure can deform the membrane and affect the zero-order delivery rate. Therefore, the cross-sectional area of the orifice S should be maintained between the minimum and maximum values. Typically ,a diameter of about 0.2 mm through a membrane of 0.2mm thickness is needed to maintain a delivery rate on the order of 10 mg/h for water-soluble compounds. The minimum cross-sectional area can be estimated from the following equation: $S_{min} = 5\left[\left(\frac{L}{P_{max}}\right)\mu\left(\frac{dV}{dt}\right)\right]^{1/2}$

Where $\frac{dV}{dt}$ = volume flux through the orifice , L = length of the orifice (usually the same as the thickness of the membrane) , μ = viscosity of the drug solution flowing through the orifice , P_{max} = maximum tolerated hydrostatic pressure difference across the membrane before the occurrence of deformation of the housing.

The maximum cross-sectional area of the orifice is obtained by specifying that the diffusional contribution to the release rate must be smaller than a fraction f of the zero-order pumping rate and is defined by the following equation: $S_{max} = \frac{M_{tz} f L}{D_S C_S}$

where M_{tz} is the amount of the drug delivered in zero-order fashion, and DS is the drug diffusion coefficient in the permeating solvent.In practice,a fraction smaller than 0.025 generally is necessary to minimize diffusionalcontributions[5].

Solubility

Solubility is the most important factor affecting the design of drug delivery.The release rate of the drug depends on the solubility of the solute inside the drug delivery system. Therefore, drugs should have sufficient solubility to be delivered by osmotic delivery. In the case of low-solubility compounds, several alternate strategies may be employed. Broadly, the approaches can be divided into two categories.

- Swellable polymers can be added that result in the delivery of poorly soluble drugs in the form of a suspension.
- The drug solubility can be modified employing different methods such as cocompression of the drug with other excipients, which improve the solubility.

For example, cyclodextrin can be included in the formulation to enhance drug solubility.Additionally, alternative salt forms of the drug can be employed to modulate solubility to a reasonable level. In one case, the solubility of oxprenolol is decreased by preparing its succinate salt so that a reduced saturation concentration is maintained[6].

OsmoticPressure

The osmotic pressure π expressed in Eq. (5)directly affects the release rate. To achieve a zero-order release rate,it is essential to keep π constant by maintaining a saturated solute solution. Many times, the osmotic pressure generated by the saturated drug solution may not be sufficient to achieve the required driving force. In this case, other osmotic agents are added that enhance osmotic pressure. For example, addition of bicarbonate salt not only provides the necessary osmotic gradient but also prevents clogging of the orifice by precipitated drug by producing an effervescent action in acidic media[7].

Methods to create a delivery orifice:

- Mechanical drill
- Laser drilling : CO_2 laser beam
- Use of modified punches
- Use of pore formers : used in controlled porosity osmotic pump

Semi Permeable Membrane (SPM)

Since the semipermeable membrane is permeable to water and not to ions, the release rate is essentially independent of the pH of the environment.Additionally, the drug dissolution process takes place inside the delivery system, completely separated from the environment.Additionally, the drug dissolution process takes place inside the delivery system, completely separated from the environment[6].

Components of Osmotic Systems

1. **Drug :** Drug which have short biological half-life(2-6 hrs), highly potent and which is used for prolonged treatment are ideal candidate for osmotic systems.Various drug candidates such as Diltiazem HCl,Carbamazepine, Metoprolol,Oxprenolol,Nifedipine,Glipizide,verapamil etc are formulated as osmotic delivery.
2. **Osmotic Agent:** 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, or sulfates of sodium or potassium and lithium. Additionally, sugars such as glucose, sorbitol,or sucrose or inorganic salts of carbohydrates can act as osmotic agents.

Hydrophilic polymers encompass osmopolymers, osmogels, or hydrogels. These materials 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.The polymers may be formulated along with poly(cellulose), osmotic solutes, or colorants such as ferric oxide. Swellable polymers such as poly(alkylene oxide), poly(ethylene oxide), and poly (alkalicarboxymethylcellulose) are also included in the push layer of certain osmotic systems. Further, hydrogels such as Carbopol (acidic carboxypolymer), Cyanamer (polyacrylamides), and Aqua-Keeps (acrylate polymer polysaccharides composed of condensed

glucose units such as diester cross-linked polygluran) may be used[8]. Finally, tableting aids such as binders, lubricants, and antioxidants may be added to aid in the manufacture of the osmotic systems.

3. **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 aluminium silicate, polyester and polyethylene.

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 pore forming 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, mannitol and, diols and polyols such as poly hyric alcohols and polyvinyl pyrrolidone can be used as pore forming agents[9].

5. **Coating solvent :** For making polymeric membrane, suitable solvent should be used. There are various organic and inorganic solvent are available. Solvents should not be toxic, should not be alter the chemical nature of polymer, should be solubilise to polymer completely. Some examples of solvents are acetone,isopropyl alcohol, ethanol, methanol, carbon tetrachloride, water, ethyl acetate,cyclohexane,butyl alcohol. The mixture of solvent like, acetone-ethanol, methylene chloride-methanol, acetoneisopropyl alcohol, acetone-water, methylene choloride-methanol-water.
6. **Fluxregulators :** 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.
7. **Platicizers :** To give the semipermeable membrane flexibility, plasticizers such as phthalates (dibenzyl, dihexyl, or butyl octyl), triacetin, epoxidized tallate, or tri-isoctyl trimellitate are added[8]. In the design of osmotic controlled release systems, these plasticizers help to modulate and achieve the required release rate.
8. **Semi Permeable Membrane: a**n important part of the osmotic drug delivery system is the semipermeable membrane housing.Therefore, the polymeric membrane selection is key to the osmotic delivery formulation. The membrane should possess certain characteristics, such as impermeability to the passage of drug and other ingredients present in the compartments. The membrane should be inert and maintain its dimensional integrity to provide a constant osmotic driving force during drug delivery[9].

Any polymer that is permeable to water but impermeable to solute can be used as a coating material in osmotic devices. e.g. Cellulose esters like cellulose acetate, cellulose acetate butyrate, cellulose triacetate and ethyl cellulose and Eudragits.

The membrane must possess certain performance criteria such as

•The membrane should be stable to both outside and inside environments of the device.
•The material must possess sufficient wet strength (10-5 Psi) and wet modules so (10-5 Psi) as to retain its dimensional integrity during the operational lifetime of the device.
•It must exhibit sufficient water permeability so as to attain water flux rates (dv/dt) in the desired range. The water vapour transmission rates can be used to estimate water flux rates.
•It must be sufficiently rigid so as to withstand the pressure within the device, to retain its dimensional integrity during the operational lifetime of the device.
•The reflection coefficient (σ) or "leakiness" of the osmotic agents should approach the limiting value of unity. But polymer membranes must be more permeable to water.
•It should also be relatively impermeable to the contents of dispenser so that osmogent is not lost by diffusion across the membrane[10].
•It should be non- swelling.
•It should be biocompatible.

TYPES OF OSMOTIC PUMPS

ORAL OSMOTIC PUMP
SINGLE CHAMBER OSMOTIC SYSTEM : Single compartment. In this design, the drug and the osmotic agent are located in the same compartment and are surrounded by the semipermeable membrane (SPM). Both the core components are dissolved by water, which enters the core via osmosis.
•Mechanism of Action: Imbibes water through the SPM because of the osmotic pressure gradient and forms a saturated solution inside the device. This increases the hydrostatic pressure inside the tablet and forces the saturated drug solution through the orice present in the membrane.
•Limitation : The dilution of drug solution with the osmotic solution, which affects the release rate of the drug from the system. Additionally,water-incompatible or water-insoluble drugs cannot be delivered effectively from a single-compartment configuration[11].
ELEMENTARY OSMOTIC PUMP : The elementary osmotic pump is a new and modified version of traditional osmotic pump. It is possible to deliver the drug by an osmotic process at a predetermined controlled rate visa two controls: semi permeable membrane and osmotic properties of formulation. The simplest elementary osmotic system is constructed by coating an osmotically active agent with the rate controlling semi permeable membrane. The membrane contains an orifice of critical size through which drug is allowed to release.
•Mechanism of Action : When the dosage form comes in contact with aqueous fluids, the water imbibes at a rate determined by the fluid permeability of the membrane and osmotic pressure of the core formulation. This results in osmotic imbibitions of water from a saturated solution of drug within the core and then saturated solution of drug is dispensed at controlled rate from the delivery orifice in the membrane. It was observed that the 60 -80 % of drug is released at a constant rate from the EOP, a lag time of almost 30-60 minute is also observed in most of the cases because the system need hydration time before zero order delivery from the system begins[1].
MULTI CHAMBERED OSMOTIC PUMPS: Multiple compartments. In this design, drug is separated from the osmotic compartment by an optional flexible film.
•Mechanism of Action : When the flexible film is displaced by the increased pressure in the surrounding osmotic compartment, which, in turn, displaces the drug solution or suspension.It inherently has greater utility than single chamber osmotic systems and can deliver drugs at a desired rate independent of their solubilities in water.
•Advantage : Their ability to deliver drugs that are incompatible with commonly used electrolytes or osmotic agents[12].

PUSH-PULL OSMOTIC PUMPS: Push pull osmotic pump is a modification of EOP. This system is similar as a standard bilayer coated tablet where one layer contains drug in a formulation of polymeric, osmotic agent and other tablet excipients. After the coating has been applied, a small hole is drilled through the membrane by a suitable method such as laser or mechanical drill on the drug layer side of the tablet[13].

•Mechanism of Action : When the dosage form comes in contact with the aqueous environment, both compartments imbibe water simultaneously. Because the lower compartment is devoid of any

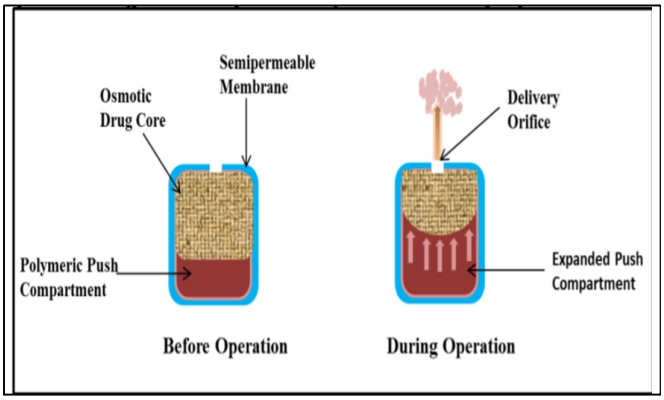


Fig.3: Push-Pull Osmotic Pump

orice, it expands and pushes the diaphragm into the upper drug chamber, thereby delivering the drug via the delivery orice.

•Advantage : It is possible to deliver both poorly water-soluble as well as highly water soluble drugs at a constant rate[13].

SANDWICHED OSMOTIC PUMP :

In this type of a system, polymeric push layer is sandwiched between two drug layers with two delivery orifices.

•Mechanism of Action : When it is placed in the aqueous environment, the middle push layer that contains the swelling agent will swell and finally the drug is released from the two orifices situated on opposite sides of the tablet. SOTS can be suitable for drugs prone to cause local irritation of the gastric mucosa.

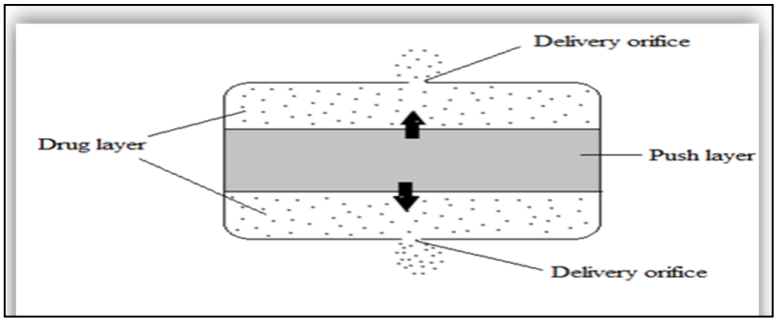


Fig.4: Sandwiched Osmotic Pump

OSMOTIC PUMP WITH NON EXPANDING SECOND CHAMBER : This system is also belongs to multi-chamber devices. The major difference from the above system is that it contains a non-expanding second chamber. The first chamber contains a biologically inert osmotic agent, such as sugar or a simple salt like sodium chloride, whereas the second chamber contains the drug.

•Mechanism of Action : In the cases where because in some of the drug leaves the oral osmotic devices a saturated solution and thus irritation of GI tract may occur. The device is useful for the delivery of relatively insoluble drugs.

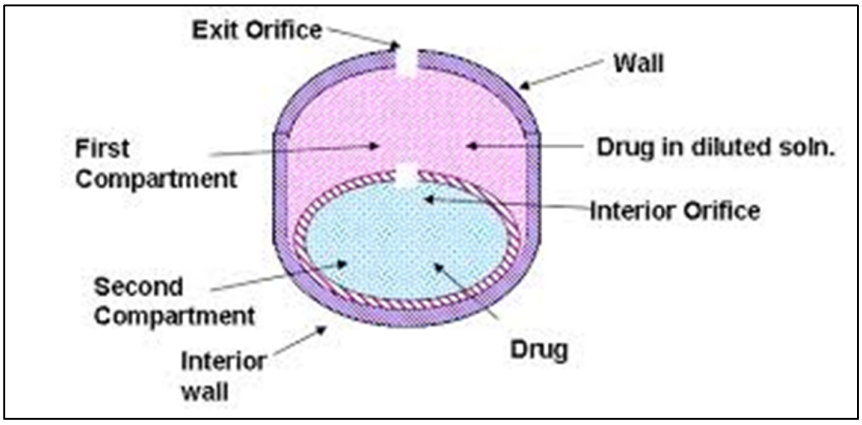


Fig.5: Osmotic Pump with non expanding second chamber

ROSE-NELSON PUMP : The Rose-Nelson implantable pump is composed of three chambers: a drug chamber, a salt chamber holding solid salt, and a water chamber.

•Mechanism of Action : A semipermeable membrane separates the salt from water chamber. The movement of water from the water chamber towards salt chamber is influenced by difference in osmotic pressure across the membrane. Conceivably, volume of salt chamber increases due to water flow, which distends the latex diaphragm dividing the salt and drug chambers: eventually, the drug is pumped out of the device.

The kinetics of pumping from Rose Nelson pump is given by the following equation: $\frac{dMt}{dt} = \left(\frac{dV}{dt}\right) \cdot C$,

where $\frac{dMt}{dt}$ is the drug release rate, $\frac{dV}{dt}$ is the volume flow of water into the salt chamber, and C represents the concentration of drug in the drug chamber.

$$\frac{dMt}{dt} = A\theta\Delta\pi\left(\frac{C}{l}\right)$$

where, A is the area of semi permeable membrane, $\Delta\pi$ is the osmotic pressure gradient, θ is the permeability of semipermeable membrane, and l is the thickness of semi permeable membrane.These basic equations are applicable to the osmotically driven controlled drug delivery devices. The saturated salt solution created a high osmotic pressure compared to that pressure required for pumping the suspension of active agent. Therefore, the rate of water entering into the salt chamber remains constant as long as sufficient solid salt is

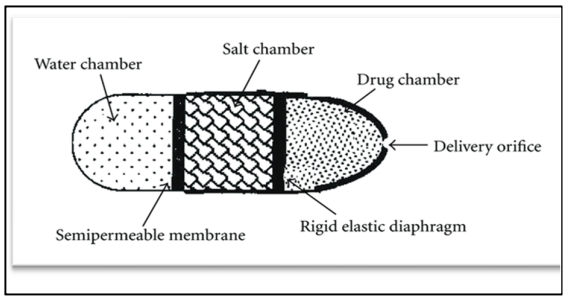


Fig.6: Rose Nelson Osmotic Pump

present in die salt chamber to maintain a saturated solution and thereby a constant osmotic pressure driving force is generated.

•Limitation : The major problem associated with Rose-Nelson pumps was that the osmotic action began whenever water came in contact with the semipermeable membrane. This needed pumps to be stored empty and water to be loaded prior to use[14].

HIGUCHI-LEEPER OSMOTIC PUMP : Higuchi and Leeper have proposed a number of variations of the Rose-Nelson pump and these designs have been described in US patents, which represent the first series of simplifications of the Rose-Nelson pump made by the Alza Corporation.

The Higuchi-Leeper pump has no water chamber, and the activation of the device occurs after imbibition of the water from the surrounding environment. This variation allows the device to be prepared loaded with drug and can be stored for long prior to use. Higuchi-Leeper pumps contain a rigid housing and a semi permeable membrane supported on a perforated frame; a salt chamber containing a fluid solution

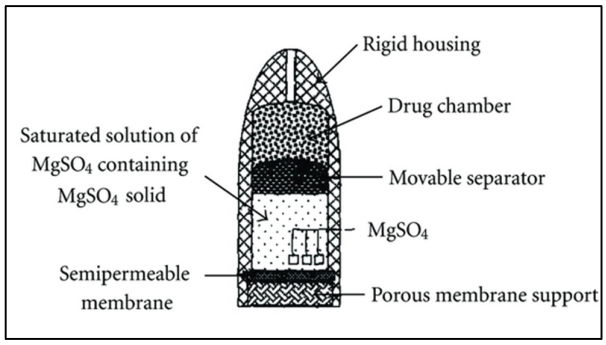


Fig.7: Higuchi Leeper Osmotic Pump

with an excess of solid salt is usually present in this type of pump.

•Mechanism of Action : Upon administration/implantation, surrounding biological fluid penetrates into the device through porous and semipermeable membrane and dissolves the $MgSO_4$, creating osmotic pressure inside the device that pushes movable separator toward the drug chamber to remove drug outside the device.

•Advantage : It is widely employed for veterinary use. This type of pump is implanted in body of an animal for delivery of antibiotics or growth hormones to animals [15].

ALZET PUMP:

Small osmotic pumps of this form are available under trade name Alzet made by Alza Corporation in 1976.

•Mechanism of Action : They are used frequently as implantable controlled release delivery systems in experimental studies requiring continuous administration of drugs.

ALZET minipumps can be used for systemic administration when implanted subcutaneously or intraperitoneally. They can be attached to a catheter for intravenous, intracerebral, or intra-arterial infusion. ALZET pumps can also be used for targeted delivery, where the effects of a drug or test agent are localized in a particular tissue or organ, by means of a catheter.

•Advantages : ALZET pumps have been used to target delivery to a wide variety of sites including the spinal cord, spleen, liver, organ or tissue transplants, and wound healing sites.

ALZET pumps have been used in thousands of studies on the effects of controlled delivery of a wide range of experimental agents, including peptides, growth factors, cytokines, chemotherapeutic drugs, addictive drugs, hormones, steroids, and antibodies.

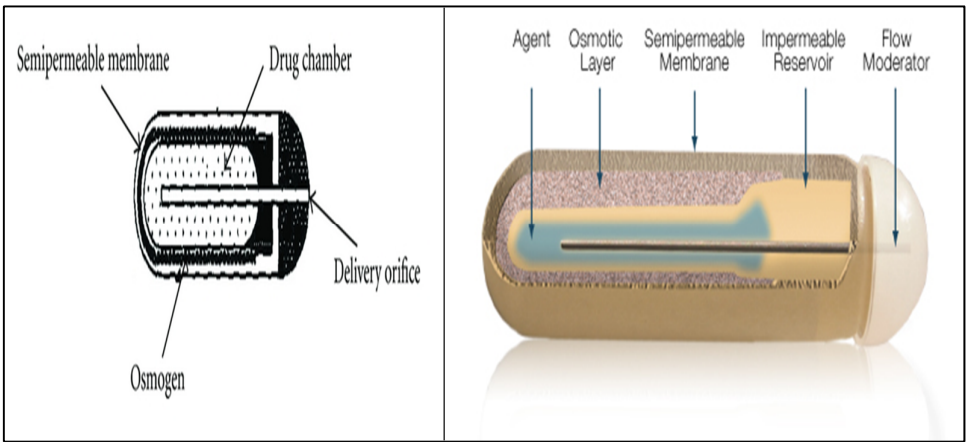
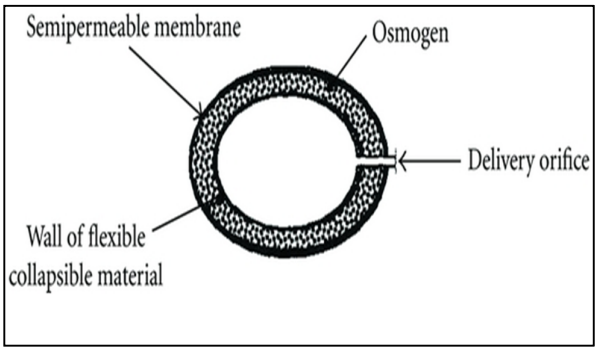


Fig.8: Alzet Osmotic Pump

•Limitation : Due to the unique mechanism by which ALZET pumps operate, compounds of any molecular conformation can be delivered predictably at controlled rates, independent of their physical and chemical properties.

HIGUCHI-THEEUWES OSMOTIC PUMP : Higuchi and Theeuwes in early 1970s developed another variant of the Rose-Nelson pump, even simpler than the Higuchi-Leeper pump.In this device, the rigid housing consisted of a semipermeable membrane. This membrane is strong enough to withstand the pumping pressure developed inside the device due to imbibition of water.



•Mechanism of Action : The drug is loaded in the device only prior to its application, which extends advantage for storage of the device for longer duration. The release of the drug from the device is governed by the salt used in the salt chamber and the permeability characteristics of the outer membrane [16].

Fig.9: Higuchi Theeuwes Osmotic Pump

MONOLITHIC OSMOTIC PUMPS TABLET : In the monolithic osmotic system, it has a simple water-soluble agent which disperses in polymer matrix.

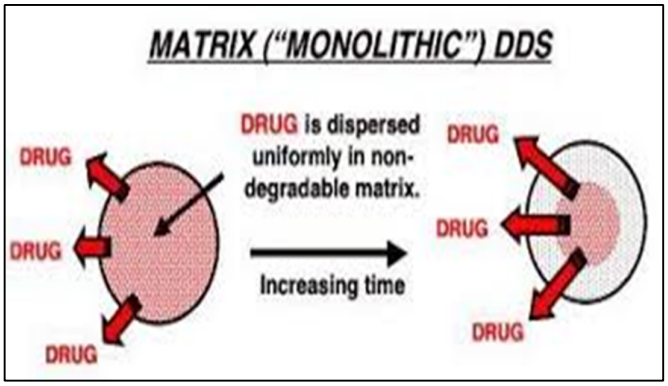


Fig.10: Monolithic Osmotic Pump

• Mechanism of Action : When the system come in contact with the aqueous environment, water imbibitions by the active agent takes place. This leads to rupturing of the polymer matrix capsule surrounding the drug. Thus drug liberation takes place to the outside environment. However, it was observed that this system fails if more then 20 –30 volumes per litre of the active agent is incorporated in to the device.

•Limitation : It fails may be because of as above this level, significant contribution from the simple leaching of the substance take place[17].

OSMOTICALLY BRUSTING OSMOTIC PUMP : This system is very similar to an EOP system. But it differs from EOP because the delivery orifice is absent and size may be smaller in this system.

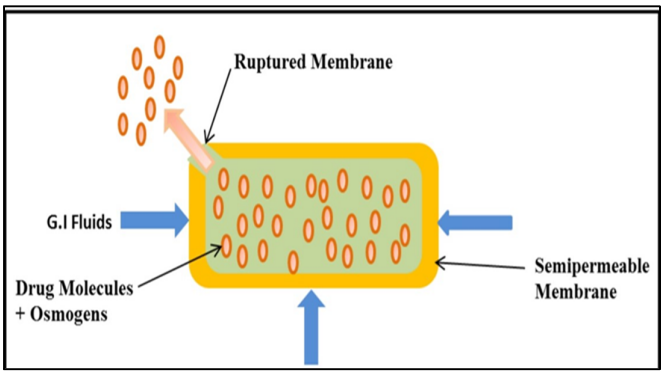
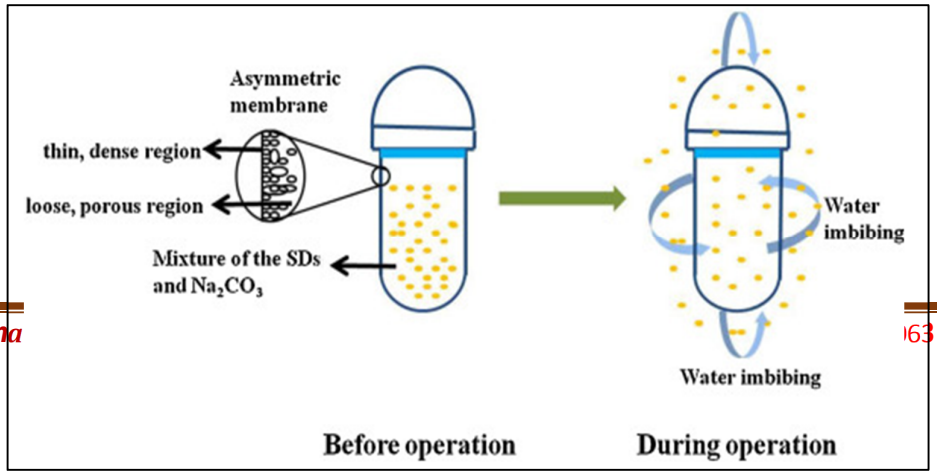


Fig.11: Osmotically brushing Osmotic Pump

•Mechanism of Action : When it is placed in an aqueous environment, water is imbibed and thus hydraulic pressure is built up inside. Due to increased hydraulic pressure inside, in order to release the pressure the wall will rupture and the drug is released to the outside of the environment. In order to control the drug release and to obtain desired drug release, the thickness as well as the area of the semi permeable membrane can be varied.

•Advantages : This type of system is able to provide drug release in pulse manner.

ASYMMETRICAL MEMBRANE OSMOTIC TABLET : Asymmetric membrane capsules consist of a drug containing core surrounded by a membrane



which has an asymmetric structure i.e. it has a relatively thin, dense region supported on a thicker, porous region. The capsule wall is made from a water insoluble polymer such as cellulose acetate unlike a conventional gelatin capsule;

•Mechanism of Action: The asymmetric membrane capsule does not dissolve immediately but provides prolonged release of the active ingredient incorporated in the capsule[18].

Fig.12: Asymmetrical Membrane Osmotic Tablet

EFFERVESCENT OSMOTIC PUMP TABLET:

•Mechanism of Action : In this system,effervescent compound are incorporated into dosage form which react with acid in the outer environment produce the carbon dioxide. This gas expands and dispenses the precipitate drug and prevents the blockage of orifice.

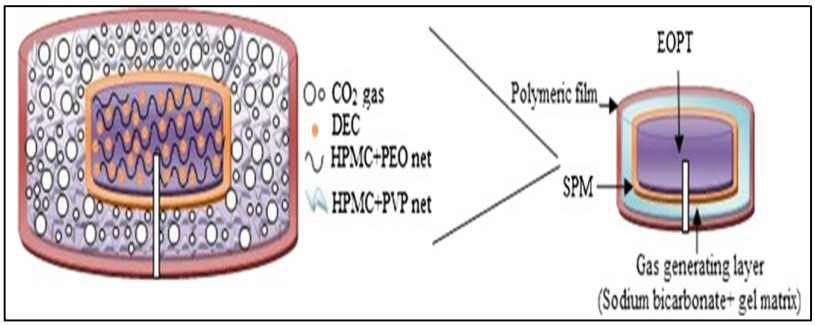


Fig.13: Effervescent Osmotic Pup Tablet

This system beneficial for poorly soluble drug at low pH may precipitate at the gastric pH and block the delivery orifice. Sodium bicarbonate is usually use in this system[19].

MULTI-PARTICULATE DELAYED-RELEASE SYSTEM (OSMOTIC PELLET) : In this system, pellets containing pure drug with or without osmotic agent are coated with a semipermeable membrane like cellulose acetate.

•Mechanism of Action : When this system comes in contact with the aqueous environment, water penetrates into the core and forms a saturated solution of soluble components. The osmotic pressure gradient induces a water influx, leading to rapid expansion of the membrane and formation of the pores. The release of osmotic ingredient(s) and the drug through these pores tend to follow zero-order kinetics. Schultz and Kleinebudde studied, lag time and dissolution rates which are dependent on the coating level and osmotic properties of the dissolution medium[20].

Newer Technologies

Ensotrol Technology : Ensotrol technology uses the same principle to deliver drugs via osmotic mechanism. The drug is mixed with solubility modifier like wicking agents. It increases the surface area creating network of channel inside the core.

Portab System (Andrx Pharmaceuticals) :PORTAB has an osmotic core, typically containing a water-soluble drug. The core includes a water soluble component and a continuous polymer coating. The purpose

of the soluble agent is to expand the core and thereby creating microporous channels through which the drug is released.

Zeros Tablet Technology (ADD Drug Delivery Technologies AG, Switzerland) : The technology is used for lipophilic drug. It comprises of drug, excipients, gel forming agents. When fluid imbibes gel formation occurs with certain viscosity drug suspension is formed pushed out through the orifice.

The Port System (Therapeutic system research laboratory Ann Arbor, MI, USA) : This capsule has three parts an active drug with osmotic agents, a slidable partition and a immediate release drug .These all are encased by a semi-permeable membrane. At the fluid entry drug with an osmotic agents gets expanded creating osmotic pressure directly push the slider made of non-swellable polymer plug causing immediate release of drug after a lag time. This is suitable for continuous delivery of drug. Example methylphenidate for the treatment of attention deficit hyperactivity disorder in school age children.

DURIN Technology : DURIN technology use biodegradable polyester like lactide glycolide co-polymer as an excipient mixed with the drug for implantable drug formulation. It can load up to 70-80% of drug. Wide variety of drugs including hydrophobic, hydrophilic drug can be used. These esters get degraded by hydrolysis after drug release and are fully absorbed by tissues. The drug and excipients are mixed formed into rods, fiber, tablet.

For example, Zoladex- goserelin used for prostate cancer have been successfully developed implants in which the membrane includes a pore forming agent that will leach out upon exposure to an aqueous environment, creating a micro porous membrane The DURIN technology has successfully achieved controlled, zero-order drug release for up to 6 months in vivo.

Volume Amplifier Delivery Devices : One of the limitations of controlled-release devices and especially with osmotic devices is the incomplete release of the drug. The release rate decreases after ~80% of the drug has been delivered. The use of volume amplifiers to deliver the entire drug contained in the system is disclosed in Patents US4331728 (1982) and US4203439 (1980).The device consists of a core, an SPM, and a delivery orifice.

Evaluation methods for Osmotic Pump Drug Delivery System

a) *In vitro* Delivery Rate Measurements

There are number of methods available for the determination of in-vitro delivery rate of drug(s) from the osmotic drug delivery systems. In loosely woven mesh bags of nylon or polyethylene, osmotic pumps are placed and the bags are attached to a rod, which in turn is attached to a horizontal transfer arm connected to a vertically reciprocating shaker.The arms containing several systems are then positioned over either on test tubes or containers that already have a known amount of release media into it. The temperature of the medium is kept constant (37°C ± 0.5°C) by using a temperature-controlled water bath. Now, as the shaker is started, the systems are immersed in the release media and stirred vertically. After acertain pre-fixed period (1–2 hr), the systems are removed from the first receptor container and then it is moved (either manually or automatically) to a second receptor container, and the stirring is continued. This same procedure continues until the systems are tested for a fixed period of about 12–24 hr depending upon dosage form and formulation. Now, each receptor solution is then analysed for the drug content by suitable method.The release rate (mg/hr) can be determined by dividing the amount of drug in each container by the time (in hours) of the test interval. And thus, the cumulative amount released is determined by adding the amounts from the various intervals. As discussed earlier that the drug release from the osmotic system follows the zero-order release profile. Thus, using least squares method of analysis the cumulative amount of drugs released from the optimized system at different time intervals are fitted to zero order kinetics to find out whether the drug release from the systems provides a constant drug release pattern or not.

b) *In vivo* Delivery Rate Measurements

It was observed that the environment in the intestinal tract of the dog is very similar to that of human beings in terms of both pH and motility.Thus, the dogs have been used widely for In vivo delivery rate measurement of drug from the osmotically controlled oral drug delivery system. To establish In vitro-In vivo Correlation (IVIVC), gastrointestinal transit of an osmotic tablet is measured by radio labeling an intact osmotic tablet which is placebo osmosin tablets. It is monitored for the movement of the unit in the GI tract of young and old healthy volunteers using gamma scintigraphy technique.

Conclusion

Drug delivery using the various OROS products can result in an improved safety profile, stable drug concentrations, uniform drug effects, and reduced dosing frequency. OROS technology has also enabled the use of an effective starting dose, without the need for dose titration, which allows the achievement of symptom control much earlier than that observed with immediate-release preparations. Such attributes can enhance patient compliance and convenience, thereby ensuring efficacy and improving patient outcomes.

Therefore, most of the currently marketed products are based on drugs used in long-term therapies for diabetes, hypertension, attention-deficit disorder, and other chronic disease states. Besides oral osmotic delivery systems, implants that work on osmotic principles are promising for delivery of a wide variety of molecules with a precise rate over a long period of time. Further, with the discovery of newer and potent drugs by the biotechnology industry, the need to deliver such compounds at a precise rate certainly will pave the way for osmotic delivery systems to play an increasingly important role in drug delivery.

References

1. Theeuwes F., Swanson D., Wong P., BonsenP.V., Heimlich K., Kwan K.C. 1983.Elementary osmotic pump for indomethacin.Journal of Pharmaceutical Sciences. 72 (3):253–258.
2. Bhatt P. 2004. Osmotic drug delivery Systems for Poorly Soluble Drugs. The Drug Delivery Companies Report Autumn/Winter.PharmaVentures Ltd. 26-29.
3. Eckenhoff, Yum SI. The osmotic pump: novel research tool for optimizing drug regimen.Biomaterials, 1981; 2:89-97.
4. Theeuwes F., and Higuchi T. Osmotic dispensing device for releasing beneficial agent, ALZA Corporation, Palo Alto, CA, U.S. Patent 3,845,770, 1974.
5. Theeuwes F., and Higuchi T. Osmotic dispensing device with maximum and minimum sizes for the passageway, U.S. Patent 3,916,899, 1975.
6. Theeuwes F., Swanson D.R., Guittard G,.Osmotic delivery systems for the beta-adrenoceptor antagonists metoprolol and oxprenolol: Design and evaluation of systems for once-daily administration.Br. J. Clin. Pharmacol, 1985;19: 2:69S–76S.
7. Santus G., and Baker R. W. Osmotic drug delivery: Areview of the patent literature.J. Contr. Rel. 35(1):1–21, 1995.
8. Wong P. S. Controlled release liquid active agent formulation dosage forms, Alza Corporation, Palo Alto, CA, U.S. Patent 6,596,314, 2003.
9. Khavare N.B., Fatima S. D., Najundaswamy N.G. 2010. A Review on Key Parameters and Components in Designing of Osmotic Controlled Oral Drug Delivery Systems. Indian Journal of Novel Drug delivery. 2(4): 122-131.
10. Jensen J.L., Appel L.E., Clair J.H., ZentnerG.M. 1995.Variables that affect the mechanism of drug release from osmotic pumps coated with acrylate/methacrylate copolymer latexes. Journal of Pharmaceutical Sciences. 84 (5): 530-533.
11. Malaterre V.; Ogorka J.; Loggia N.; and Gurny R. “Approach to design push–pull osmotic pumps.” International journal of pharmaceutics 376.1-2, (2009): 56-62. Print.
12. Theeuwes F. Elementary osmotic pump. J. Pharm. Sci. 64:1987–1991, 1975.

13. Malaterre V., Metz H., Ogorka J., Mader K., Gurny R., Loggia N. Influence of the hydration kinetics and the viscosity balance on the drug release performance of push-pull osmotic systems. Novartis Pharma AG, Technical R&D, Fabrikstrasse 2, CH4056 Basel, Switzerland, 1-2.2009.
14. Rose S. and NelsonJ. F., "A continuous long-term injector," The Australian Journal of Experimental Biology and Medical Science, vol. 33, no. 4, pp. 415–419, 1955.
15. Higuchi T., "Osmotic dispenser with collapsible supply container," US Patent No. 3, 760,805, 1973.
16. Wong P. S. I.,Barclay B., Deters J. C., and Theeuwes F., "Osmotic device with dual thermodynamic activity," US Patent 4612008, 1986.
17. Xing-Gang Y., Guo-Hua Z., Wei L., BoP., Zhi-Dong L., Wei-San P. 2006. Design and Evaluation of Jingzhiguanxin Monolithic Osmotic Pump. Chem. Pharm. Bull. 54(4): 465-469.
18. Verma R. K.; D. M. Krishna; and S. Garg. "Formulation aspects in the development of osmotically controlled oral drug delivery systems."Journal of Controlled Release 79.1-3, (2002): 7-27. Print.
19. Xio-dong Lee, Wei-san Pan, Shoe-fan Lee, Li-ju Wu, 2004. Studies on controlled release effervescent osmotic pump tablet from traditional Chinese medicine compound recip, Journal of controlled release, 96: 359-367.
20. Schultz P., Kleinebudde P. 1997. A new multiparticulate delayed release system. Part I: Dissolution properties and release mechanism. Journal of Controrlled Release. 47:181-189.