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Advances in osmotic drug delivery system

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ABSTRACT

Osmotic drug delivery system (ODDS) utilizes the basic principle of osmotic pressure for controlled release of drugs. It provides the release of drugs in controlled manner to maintain drug concentration within therapeutic window and minimizing toxic effects. ODDS delivers a drug to large extent is independent of the physiological factors of the gastrointestinal tract, pH etc. That is why it can be utilized for systemic as well as targeted delivery of drugs. The drug release from osmotic system controls the drug release by controlling various formulation factors such as solubility, osmotic pressure of the core components, size of the delivery orifice and nature of the rate controlling membrane. The design of osmotic system is achieved by optimizing formulation and processing factors to deliver drugs in preprogrammed rate and controlled manner. The present study explains about an update on osmosis, different types of osmotic systems, components of ODDS, key parameter sand some patents.

Keywords: Osmotic drug delivery system, pH, Osmotic pressure, Patents.

INTRODUCTION

Treatment [1] of various diseases (acute disease or chronic disease) has been mostly accomplished by delivery of drugs to patients using various pharmaceutical dosage forms. Oral drug delivery [2,3] has been popular and most widely utilized route of administration than other routes that have been explored for the systemic delivery of drugs. Conventional oral drug delivery [4,5] system provides an immediate release of the drug and can not maintain effective concentration at the target site for longer period of time. The bioavailability of drugs by conventional drug delivery is very low due to presence of food, pH of gastro intestinal tract, degradation by enzymes of GI fluid, change in GI motility etc. For avoid these shortcomings controlled drug delivery system has taken major role in the pharmaceutical development. It offers temporal or spatial control over release of drug. This is due to improved patient convenience and compliance, reduction in fluctuation in steady state plasma level so decrease intensity of local or systematic side effects and increase safety margin of high potency drugs. In control release systems there is maximum utilization of drug enabling reduction in total amount of dose administered and possibility of delivering drugs having short biological half life [6-9].

Among various controlled drug delivery systems osmotic controlled drug delivery system[10] utilizes principle of osmotic pressure for controlled delivery of active ingredients. The drug is released from ODDS which is independent of P^H and hydrodynamic conditions of the body because of the semi permeable nature of the rate controlling membrane and the design of deliver orifice used in osmotic systems. Hence a high degree of in vitro-in vivo correlation is achieved. ODDS provides a uniform concentration of drug at the site of absorption and thus after absorption allow maintenance of plasma concentration within therapeutic range which minimizes side effects and also reduces the frequency of administration [11,12]. ODDS follow zero order kinetics for constant release of drug from an osmotic device. Osmotic pressure [13] created by osmogen is utilized as driving force for these systems to release the drug in controlled manner. When an osmotic device contacts with water, water imbibes into the core through the micro porous membrane setting up an osmotic gradient and thereby controlling the release of drug. The core comprises of a drug formulation that contains an osmotic agent and water swellable polymer. The absorption of water core depends on the osmotic pressure generated by the core components and the permeability of the membrane coating[14].The distinguishing feature of osmotic drug delivery system from other technologies used in controlled release formulations is that drug release from osmotic system is independent of pH, other physiological parameters and hydrodynamics of the external dissolution medium. Osmotic drug delivery technique is most interesting, widely acceptable among all other technologies and mostly applicable to drugs with a broad range of aqueous solubilities. The route of administration of ODDS may be oral and parental. Oral osmotic systems are known as gastro intestinal systems and parental osmotic systems are known as implantable pumps [15,16].The present review gives idea about osmosis, osmotic drug delivery devices, key parameters for designing of osmotic drug delivery systems, basic components of osmotic pumps, advantages and disadvantages.

OSMOSIS

Osmosis refers the process of spontaneous movement [17] of a solvent from a solution of lower solute concentration to a solution of higher solute concentration through an ideal semi permeable membrane which is permeable only to the solvent but impermeable to solute. It is driven by a difference in solute concentrations across the membrane that allows passage of water, but rejects most solute molecules or ions. Osmosis is the phenomenon that makes osmotic controlled drug delivery in a reality. Osmotic pressure is the pressure applied to the higher concentrated solution side to prevent transport of water across the semi permeable membrane. Osmotic pressure is created due to imbibitions of fluid from external environment into the dosage form regulates the delivery of drug from osmotic devices [18]. Rate of drug delivery from osmotic system is directly proportional to the osmotic pressure developed due to imbibitions of fluids by osmogen. Osmotic pressure is a colligative property [19] of a solution where magnitude of osmotic pressure of the solution is independent on the number of discrete entities.

Jean Antoine Nollet reported the first osmotic effect in 1748.Pfeffer [20] reported from an experiment using semi permeable membrane to separate sugar solution from pure water in 1877 that the flow of water takes place into the sugar solution until an osmotic pressure is applied to sugar solution to resist its flow. Hence he observed that due to osmosis the water was flowing to higher solute concentration of sugar solution. Finally he observed that osmotic pressure of the sugar solution is directly proportional to the solution concentration and the absolute temperature. But Jacobus Henricus Van't Hoff modified the equation for osmotic pressure [21,22]. He obtained that osmotic pressure is proportional to concentration and temperature and the relationship is described by the following equation 1.

$\pi = i\frac{n}{V}RT = iCRT$……(1)

where π is osmotic pressure of the solution is the number of moles of solute(mol),i is the Van't Hoff factor is volume of solution(L),C and R are the molar concentration of solute(mol/L) and molar gas constant($8314 Jmol^{-1}K^{-1}$) respectively and T is absolute temperature(K).The Van't Hoff factor(i) is the number of moles of solute actually dissolved in solution per mole of added solid solute i.e. equals to one if the solute does not dissociate(e.g nonelectrolytes) in water or becomes larger than one in case of dissociation occurs. Hence the number of solute molecules is more in ionic compounds. Considering α as the degree of dissociation and m as the number of ions,a solute can dissociate into I molecules according to the equation[23] given below.

$I = 1+\alpha(m-1)$……..(2)

When an osmotic system contacts with the aqueous environment or any body fluid, it imbibes with water and water will flow into the core due to osmotic pressure difference across the semi permeable membrane under the osmotic pressure gradient. The volume flow of water or water flux into the core reservoir is expressed in equation 3.

$\frac{dv}{dt}=\frac{A}{h}$L(σd π-dp)…….(3)

Where dv/dt is water flux, A is area of the semi permeable membrane, h is thickness of the membrane, $d\pi$ and dp are the are the osmotic and hydrostatic pressure difference between the inside and outside of the system,L is mechanichal permeability and σ is the reflection coefficient. The drug will be pumped out of the system through the orifice at a controlled rate is expressed in equation 4.

$\frac{dm}{dt}=\frac{dv}{dt}$C…….(4)

Where dm/dt is solute/drug delivery rate and C is the concentration of drug in dispersed fluid.

Reflection coefficient is taken to consideration when there is leakage of drug through the membrane. The SPM which is perfect does not allow solute to pass through it and σ is close to unity. If the orifice is sufficiently large the hydrostatic pressure will be negligible which tends to zero. Hence the equation 3 becomes

$\frac{dv}{dt}=\frac{A}{h}$Lσd π…….(5)

The osmotic pressure of gastrointestinal fluids is negligible as compared to that of core, hence π is replaced by dπ and Lσ is replaced by a constant K.Hence the equation becomes

$\frac{dv}{dt}=\frac{A}{h}$K π…….(6)

Hence the pumping drug rate from the core can be expressed[24,25] as

$\frac{dm}{dt}=\frac{A}{h}$K π C…….(7)

OSMOTIC DRUG DELIVERY DEVICES

The osmotic drug delivery devices generally classified into two broad categories such as implantable osmotic pump and oral osmotic pumps. These are explained below.

Implantable

Implantable type of osmotic pumps generally inserted in certain part of the animals or humans and it delivers the drug through the orifice when it is contacted with body fluid. Mainly implantable osmotic pumps are given below.

The Rose and Nelson pump

In 1955 two Australian physiologist Rose and Nelson [26] reported the first osmotic pump. They inserted this pump in the gut of sheep and cattle for the delivery of drugs. It is consisted of three chambers such as a drug chamber with an orifice, a salt chamber with elastic diaphragm containing excess solid salt and a water chamber (Fig.1). A rigid semi permeable membrane is present between the drug chamber and water chamber. The difference in osmotic pressure across the chamber causes the movement of water from the water chamber into salt chamber. The volume of salt chamber increases because of this water flow which causes the diaphragm separating salted drug chamber and pumping drug out of this device. The pumping rate of drug from Rose and Nelson pump is given by the equation

dm/dt=dv/dt*c……..(8)

where dm/dt is drug release rate, dv/dt is volume flow of water into salt chamber and c is the concentration of drug in the drug chamber.

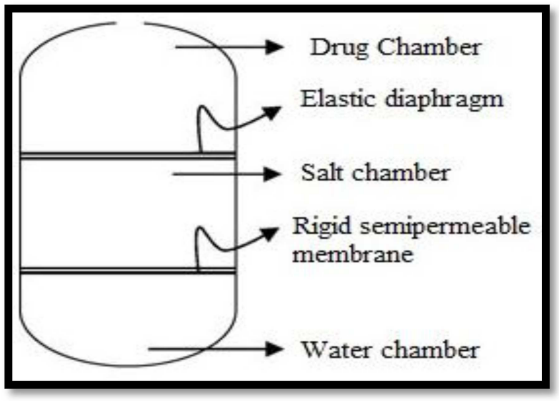

Fig. 1: Rose Nelson pump

Higuchi Leeper pump

The design of Higuchi Leeper pump is the first simplified version of Rose Nelson pump made by the Alza corporation in early 1970.The benefit of this pump is that it is devoid of contain water chamber and the pump is activated by water imbibed from the surrounding environment when it is swallowed or implanted in the body. The system consists of a rigid housing and the SPM is supported on a perforated frame(Fig.2). The pump is first prepared and then loaded with the drug and then it can be stored for weeks or months before to use[27].

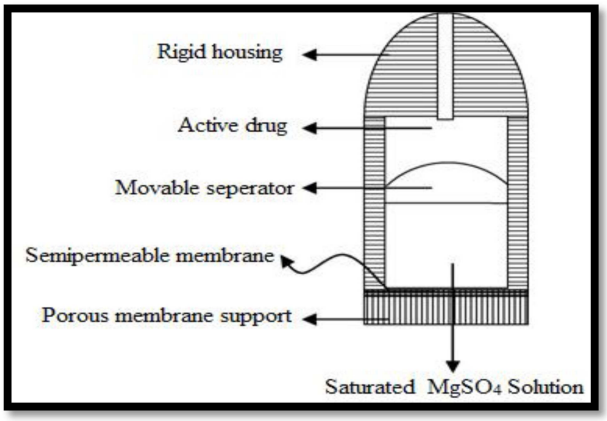

Fig. 2: Higuchi Leeper Pump

Higuchi Theeuwes pump

In early 1970 Higuchi Theeuwes pump was developed. The semi permeable membrane acts as a rigid outer casing of the pump. The device is loaded with drug before to use. In aqueous environment the pump releases the drug follows a time course set by the salt used in salt chamber and permeability of the outer membrane. The device (Fig.3) consists of an osmotic core containing the drug surrounded by semi permeable membrane with a delivery orifice. When the pump is placed in water the core imbibes water osmotically at a controlled rate determined by the membrane permeability to water and by the osmotic pressure of the core formulation. Due to pressure the flow of saturated drug solution is delivered through the delivery orifice. This process continues at a constant rate until the entire drug inside the pump has been dissolved and a solution filled coating membrane is left[28].These residual dissolved agents continue to be delivered at a declining rate until the osmotic pressure inside and outside the system is equal. It is used for delivery of dispersion of solid salt in a suitable carrier for the salt chamber of the pump.

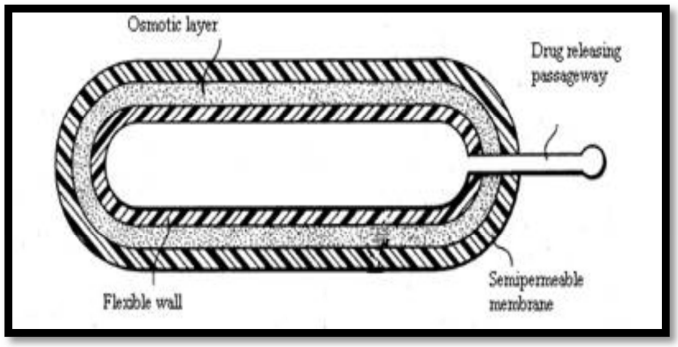

Fig. 3: Higuchi Theeuwes pump

Implantable miniosmotic pump
They are may be used in experimental animals or in human being.

Alzet
Alzet osmotic pumps are miniature, implantable pumps used for research in mice, rats and other laboratory animals. It consists of a collapsible reservoir(Fig.4) made of impermeable thermoplastic hydrocarbon elastomer which is surrounded by a coating layer of osmotic driving agent. The SPM is made of on a cellulose ester blend that overcoats the osmotic layer and forms the outer surface of the pump. In alzet osmotic pump the empty reservoir within the core of the pump is filled with the drug solution to be delivered and is surrounded by salt chamber with impermeable layer between them. When water enters to the osmotic layer it generates a pressure inside the reservoir and displaces the stored drug volume. The drug release rate is the volume of water penetrating the SPM multiplied with the concentration of the stored drug solution. The rate of drug delivery of the pump is controlled by the water permeability of the pumps of outer membrane[29].The pumps are available with three different capacities such as 100µl,200µl and 2ml with delivery rates ranging from 0.11µl/h to 10µl/h.

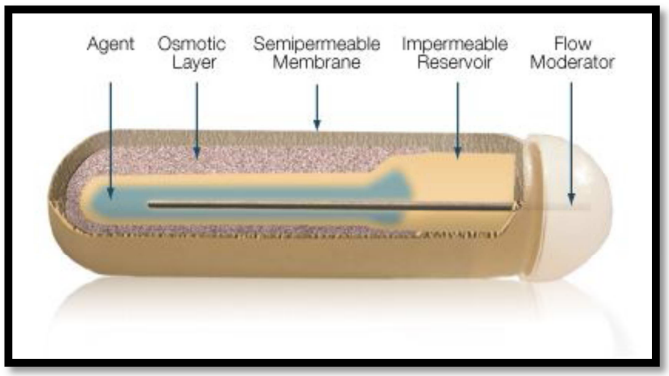

Fig. 4: Alzet osmotic pump

Duros miniosmotic pump
The DUROS system(Fig.5) was developed by ALZA Corporation which was acquired by Johnson and Johnson in 2001.It is a miniature, implantable osmotic pump for long term parenteral drug delivery in human. The system made of an outer cylindrical titanium alloy reservoir. The one end of the reservoir is positioned the membrane ,constructed from polyurethane polymer. The membrane is permeable to water and impermeable to ions. The next to membrane is the osmotic engine and next to it is piston. The piston separates the osmotic engine from the drug formulation in the drug reservoir compartment [30].At the distal end of the titanium cylinder is the exit port. Through the exit port water from the body is slowly drawn to the semi permeable membrane into the pump by osmotic agent residing in the engine compartment which expands the osmotic agent and displaces a piston to dispense small amounts of drug formulation from the drug reservoir through orifice. Depending on the composition of the semi permeable membrane the drug release can be maintained for a time period of 3 to 12 months. The device has an outside diameter of 4mm,a length of 44mm and a drug reservoir capacity 155µl.It can be inserted on the arms and abdomen in a simple outpatient procedure.

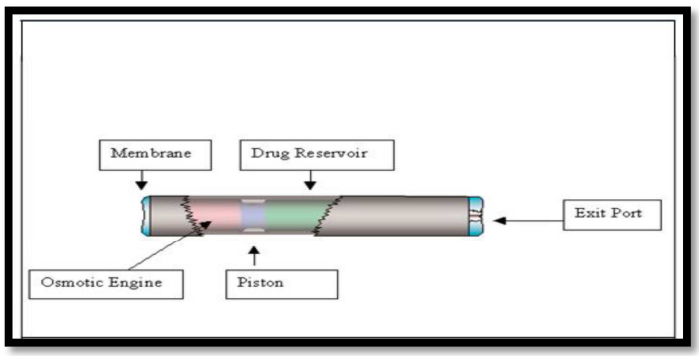

Fig. 5: Duros implantable miniosmotic pump

LiRIS®

It is a small and flexible single compartment osmotic system that can move freely in human bladder. It is introduced by Lee and Cima[31] from Massachusetts Institute of Technology. The LiRIS® Lidocaine Releasing Intravesical System is used for the treatment of interstitial cystitis and painful bladder syndrome(IC/PBS).The device is based on a double lumen medical grade PDMS tube. One part of lumen is incorporated with lidocaine tablets whrereas the other part incorporates a shape memory wire made of nitinol.By nonsurgical procedures (catheter or cytoscopy) the device is inserted as well as retrieved from the bladder. Interstices breaks between the lidocaine tablets together with the super elastic effect of the wire allow the deformation of the system into a linear shape for insertion and return to its pretzel like post insertion. After insertion of the device into the bladder the whole silicone tube operates as the semi permeable membrane and a small laser drilled orifice within its wall acts as the lidocaine release outlet.

Ivomec SR®Bolus

The pump is introduced by Merck &Co[32].,Inc,NJ,USA having a diameter of 20 to 30mm and length of about 100mm.It is generally used for veterinary purpose. It is designed to administer ivermectin directly in the lumen of cattles[33].The device is sedimented in the lumen of the animal due to its higher density(upto 3g/cm^3).The wax based piston separates the osmotic agent compartment and the drug compartment of the device. The thermoresponsive drug formulations melt at the body temperature of cattle and it is pushed out by the piston, using push melt^{TM} technology. The steady state of the drug can be maintained for 135 days with the pump.

Acuros

The pump is introduced by Humboldt University[34] Berlin,Germany.The osmoregulatory micro pump consists of a salt chamber(osmotic agent),a water chamber(solvent) and an extrusion chamber with a movable barrier displacing drug from the drug reservoir.A semi permeable hollow fiber meandering within the water chamber connects the salt chamber with the extrusion chamber. This causes water to penetrate into the fiber by osmosis and generates a convective flow inside the fiber towards the extrusion chamber. The diluted salt solution within the fiber passes the salt chamber containing higher concentrated solution. From the salt salt chamber this leads to the displacement of salt solution at this dedicated location and generates a convective flow inside the osmotic agent chamber. As a result of which a conventional recirculation is maintained that supplies the fiber continuously with highly concentrated salt solution. The majority of the diluted salt solution within the hollow fiber flows into the extrusion chamber and induces the outflow of the drug solution by displacing the movable barrier into the liquid drug reservoir.

Hydrogel pump

The pump is introduced by Richter et.al [35]..It uses poly(N-Isopropyl acrylamide) or other strong swelling super absorbent polymers as osmotic agents. The pump is activated by switching a trigger. After activation the reservoir opens and the liquid based swelling agent is provided to the hydrogel actuator. Since the reservoir is pressurized by a spring force the supply with swelling agent is independent of the spatial orientation of the device. The swelling hydrogel has first to fill a predefined volume before it starts to displace the self locking system. Hence the size of the volume determines a time delay which can be adjusted by an external screw enabling individual delays. After the piston begins to move and presses a drug ampoule against an ampoule opener. Once the drug ampoule is crushed delivery of drug through the outlet starts.

Oral osmotic pump
There are many types of oral osmotic pumps are available which are explained below.They are mainly classified into single chamber osmotic pump,multichamber osmotic pump and specified types of osmotic pumps**.**

Single chamber osmotic pump
It contains only single chamber for osmotic drug delivery system.

Elementary osmotic pump(EOP)
The elementary osmotic pump(Fig.6) was developed in 1970 which delivers the active agent by an osmotic process at controlled rate. The EOP consists of an osmotic core containing the drug surrounded by a rate controlling SPM which is laser drilled with a delivery orifice. The orifice size is critical in semi permeable membrane through which active agent is delivered. When the EOP system comes in contact with aqueous fluids it imbibes with water. The osmotic imbitions of aqueous fluid causes saturated solution of drug within the core which is dispensed at a controlled rate from the delivery orifice in the membrane. The processes go on at a constant rate until the entire solid drug inside the system has been dissolved. The drug is released upto 60-80% at a constant rate from the EOP and a lag time of 30-60 minutes is obtained. In most of the cases as the system hydrates before zero order delivery from the system begins[36].It is suitable for water soluble drugs.

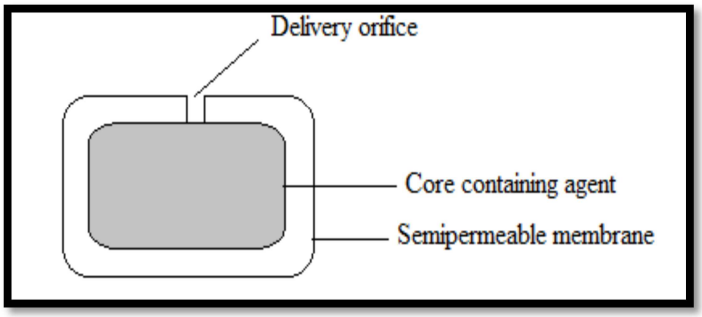

Fig. 6: Elementary osmotic pump

Multi chamber osmotic pump
It contains more than one chamber for ODDS.

Push pull osmotic pump
Push pull (Fig.7) osmotic pump is a modified EOP which delivers poorly water soluble drug at a constant rate appeared in 1980.The system contains two layers,one layer (upper layer) contains drug in a formulation with osmotic agent and another layer(down layer) contains polymeric osmogents with excipients.The PPOP system[37,38] is coated with semi permeable membrane with a delivery orifice. The SPM regulates water influx into both layers surrounds the system. When the system contacts with the aqueous fluid, polymeric osmotic layer swells and pushes the drug layer and thus releasing the drug from of fine dispersion through the delivery orifice. It is suitable for poorly water soluble drugs and highly water soluble drugs.

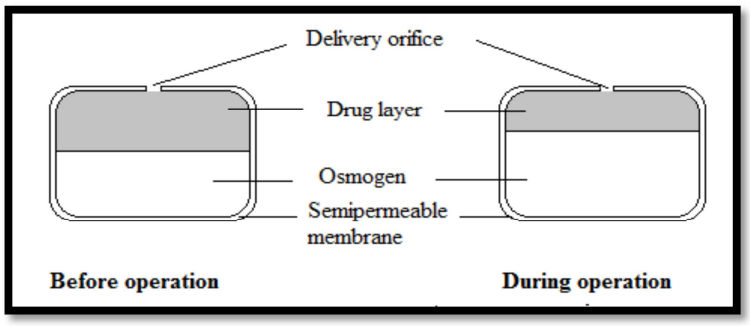

Fig. 7: Push pull osmotic pump

Osmotic pump with non expanding second chamber

It consists of a system containing a nonexpanding second chamber. The function of second chamber is either dilution of drug solution leaving the device or simultaneous delivery of two drugs. The device consists of a normal drug containing porous tablet from which drug is released as a saturated solution. This type of device consists of two rigid chamber the first chamber contains a biologically inert osmotic agent and the second chamber contains the drug. When it exposes to aqueous environment, water penetrates into both the chamber through the surrounding semi permeable membrane. Osmotic agent solution is formed in the first chamber then passes through the connecting hole to the drug chamber where it mixes with the drug solution before exiting through the micro porous membrane that form a part of wall surrounding the chamber[39].

Specific types

The specific types of ODDS are explained below.

Controlled porosity osmotic pump

The pump can be designed single or multicompartment dosage form the delivery system comprises a core with the drug surrounded by a membrane. The SPM is accomplished with different channeling agents of water soluble additives in the coating. It has an asymmetric structure supported by a porous[40,41] substructure. When CPOP(Fig.8) placed in water low levels of water soluble additives are leached from polymer materials that were permeable to water. As a result of which sponge like structure is formed in the controlled porosity walls. The membrane is permeable to both water and dissolved solutes. The rate of drug delivery depends upon the factors are water permeability of the semi permeable membrane, osmotic pressure of core formulation, thickness and total surface area of coating. The designer can control all the factors and the formulation will not change in physiological conditions [42].The rate of flow of water into the device can be expressed as given below.

$dv/dt=Ak/h(d\pi-dp)$…….(9)

where dv/dt is rate of flow of water to the device, and A are membrane permeability and surface area of membrane respectively, $d\pi$and dp are osmotic pressure difference and hydrostatic difference between inside and outside of the membrane respectively.

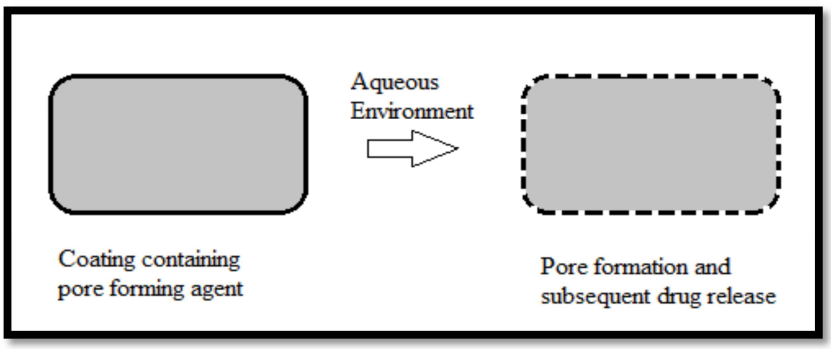

Fig. 8: Controlled porosity osmotic pump

Osmotic bursting osmotic pump(OBOP)

In OBOP system (Fig.9) the delivery orifice is absent or orifice size may be smaller. When the system is placed in an aqueous environment[43] water imbibitions takes place. Due to imbibitions hydrostatic pressure is generated inside until the wall ruptures and the contents are released to the environment. The drug release can be controlled by changing the thickness as well as the area of the SPM. The system is suitable for pulsated drug release.

Liquid OROS/Liquid oral osmotic system

Liquid OROS[44] is designed to deliver drugs of liquid formulations. The system(Fig.10) includes a liquid drug layer, an osmotic engine or push layer and a semi permeable coating. When the system is placed in the aqueous environment water penetrates across the rate controlling membrane and active the osmotic layer. The osmotic layer expands resulting the development of hydrostatic pressure inside the system and forcing the liquid formulation to be delivered from the delivery orifice.

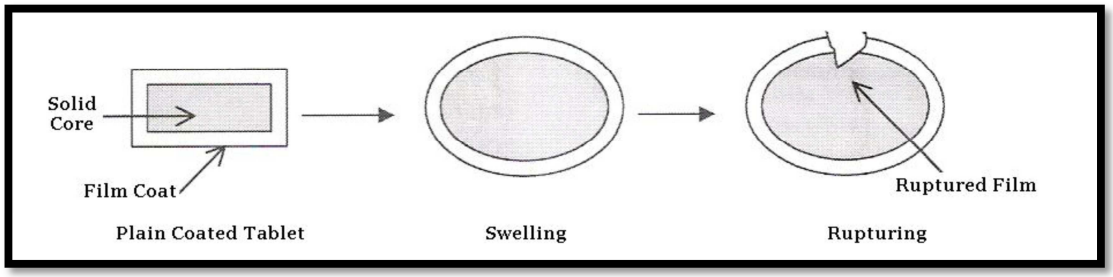

Fig. 9: Osmotic bursting osmotic pump.

L OROS hard cap

In L OROS hard cap system the liquid formulation is available in hard gelatin capsule which is surrounded with the barrier layer, the osmotic layer and the rate controlling membrane. One delivery orifice is designed through these three layers.

L OROS soft cap

The liquid drug formulation is present in a soft gelatin capsule which is surrounded with the barrier layer, the osmotic layer and SPM.A delivery orifice is designed through these three layers. When the system is exposed to the aqueous environment water is imbibed and results in the development of hydrostatic pressure inside the system forcing the liquid formulation to break through the hydrated gelatin capsule shell at the delivery orifice.

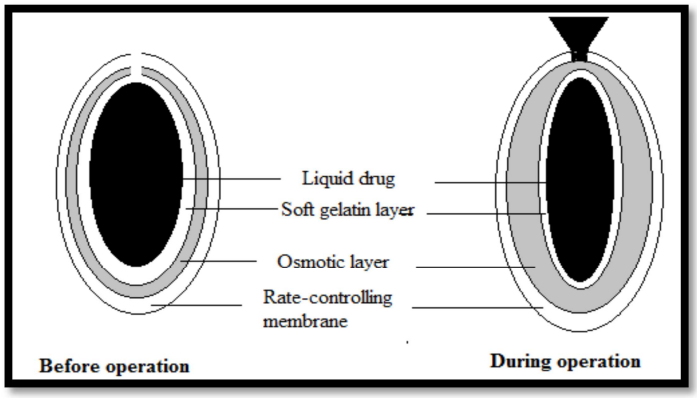

Fig. 10: Liquid OROS/Liquid oral osmotic system

Delayed liquid bolus delivery system

This system is composed of three layers a placebo delay layer, a liquid drug layer and an osmotic engine all surrounded by rate controlling SPM. The delivery orifice is drilled on the placebo layer end of the capsule shaped device. When it comes in contact with water the osmotic engine expands, the placebo is released first delaying release of drug layer. The drug release can be delayed up to 1 to 10h depending upon the permeability of SPM and thickness of placebo layer.

Telescopic capsule

This device consists of two chambers, the first chamber contains the drug and an exit port and second chamber(Fig.11) contains an osmotic engine a layer separates the two chambers. The drug is transferred into one of the section by manual or automated fill mechanism. The capsule with osmotic engine is placed into a completed cap part of the capsule with the convex osmotic layer pointed into the closed end of the cap and the barrier into closed end of the cap and the barrier layer is exposed towards the cap opening. The open end of the filled vessel is fitted inside the open end of the cap and the two pieces are compressed together until the cap, capsule and vessel fit together tightly. When the system exposes to aqueous environment, water is imbibed the housing of the dispensing device the osmotic engine expands and exerts pressure in the chamber and the drug is released. In the delay period the drug in the chamber is constant[45,46].Hence a minimum pressure gradient exists between the inside and outside

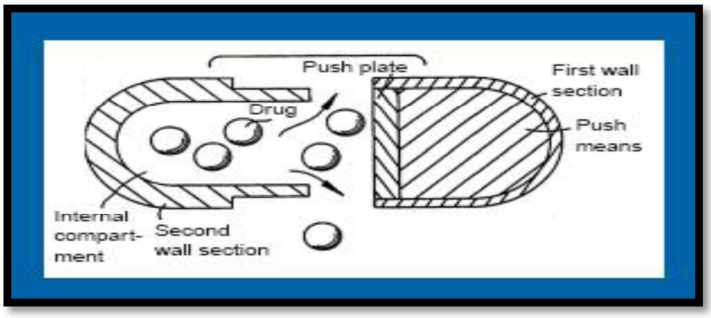

Fig .11: Telescopic capsule

OROS CT

It is developed by Alza corporation for targeted delivery of drugs is taken orally to the colon. The system may contain a single osmotic agent or as many as five to six push pull osmotic unit(Fig.12) filled in a hard gelatin capsule[47].It consists of an enteric coat, SPM and core. When the system is exposed it comes in contact with the gastric fluids, gelatin capsule is dissolved and the enteric coating prevents entry of fluids from stomach to the system as the system enters into small intestine the enteric coating dissolves and water is imbibed into the core by swelling the compartment. Simultaneously flowable gel is formed in the drug compartment which is pushed out of the orifice at a controlled rate.

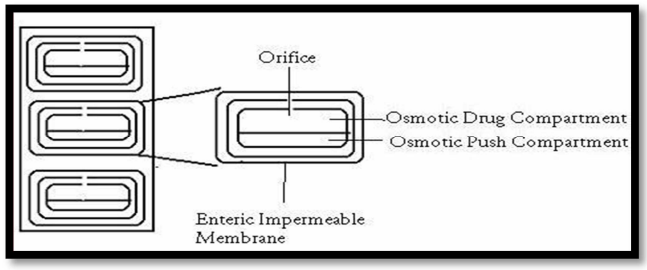

Fig. 12: OROS CT

Sandwiched osmotic tablets (SOTS)

The system is composed of polymeric push layer sandwiched (Fig.13) between two drug layers with two delivery orifices. When it is exposed in the aqueous environment the middle push layer containing the swelling agent swells and the drug is released from the two orifices situated on opposite sides of the tablet[48].Hence it can be used for drugs to cause local irritation of gastric mucosa.

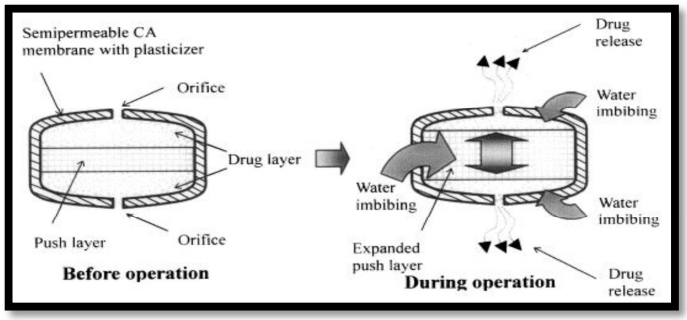

Fig. 13: Sandwiched osmotic tablets

Monolithic osmotic system

It consists of a simple dispersion of water soluble agent in polymer matrix. When the system comes in contact with the aqueous environment [49]water imbibitions by the drug takes place causing the polymer matrix capsule surrounding the drug thus of the active liberating it to the outside environment. This process occurs at the outer

environment of the polymeric matrix in aserial fashion. This system is not possible if more than 20-30 volume per liter of the active agents is incorporated into the device as above this level [50].

Osmat

Osmat system utilizes the hydrophilic polymers to swell in matrix and gel in aqueous medium forming a semipermeable membrane in situ releases from such a matrix system containing an osmogen. The system produces controlled drug release from swellable [51] matrix system. It is very simple, versatile and easy to fabricate in low cost technology.

Multi particulate delayed release systems (MPDRS)

MPDRS comprise of pellets consists of drug with or without osmotic agent, which are coated with a semi permeable membrane. When the system comes in contact with the aqueous environment, water enters in the core and forms a saturated solution of soluble component. The osmotic pressure difference results in rapid expansion [52] of the membrane and causes the formation of pores. Due to osmotic agent the drug is released through the pores according to zero order kinetics. The lag time and dissolution rate depend upon the coating level and osmotic properties of the dissolution medium.

Pulsatile delivery based on expandable orifice

The pulsatile delivery of agent from osmotic system is based on the technology of expandable orifice which delivers the drug at right site of action ,at right time and right amount. It provides spatial and temporal drug delivery. It is designed according to circadian rhythm of the body. The system is in the form of capsule from which the drug is released by the capsule's osmotic infusion of moisture from the body. The delivery orifice opens intermittently[53] to achieve a pulsatile delivery effect. The orifice is formed in the capsule wall. As the osmotic release proceeds pressure rises within the capsule causing the wall to expand. The orifice is small as a result of which when the elastic wall relaxes the flow of the drug through the orifice essentially stops, but when the elastic wall stretches beyond the threshold because of increase of pressure, the orifice expands sufficiently to allow the drug to be release at a required rate.

Pulsatile delivery by a series of stops

Alza corporation explained for implantable capsule for pulsatile delivery by a series of stops in osmotic systems. The capsule comprises of drug and absorptive osmotic agent engine that are placed in the each compartments separated by a movable partition. Pulsatile [54] delivery is obtained by a series of stop along the inner wall of capsule. These stop block the movement of the partition but overcome in succession as the osmotic pressure rises above the threshold level. The number of stops and the longitudinal placement of the stops along the length of capsule determine the number and frequency of pulses. The design of the partition controls the pulse intensity.

Lipid osmotic pump

The lipid osmotic pump device releases an osmotic agent for dispensing active agent that has poor solubility in water. The core of the system consists of water insoluble active ingredients which is lipid soluble or lipid wettable, a sufficient amount of water insoluble lipid carrier which is liquid at the temperature of use to dissolve or suspend the drug and the agent to ensure the release of the lipid carrier of drug from the pump. The wall is micro porous [55] and is wetted by by lipid carrier. The device is formulated by fast dissolving the drug in the lipid vehicle. The osmogent is melted in the lipid and then cooled to form a lump that are broken and made into tablet. The micro porous is coated at moderate flow of ambient air.

Longitudinally compressed tablet(LCT) multilayer formulation

The LCT multilayer formulation (Fig.14) is an advanced technology for osmotic drug delivery system. It consists of an osmotic push layer and can be designed to contain several drug layers. The function of multiple drug layers provides increased flexibility and control over the pattern of release of medication from the system as opposed to single layer used in the push pull system which can deliver a drug in a zero order fashion. When LCT system is exposed to water, water absorption takes place through the semi permeable tablet shell and the push compartment expands and delivers the drug primarily through the first compartment through the laser drilled orifice. After some time from the second compartment drug release starts at a different rate. It can be designed with different drugs in different layers to provide combination therapy[56].

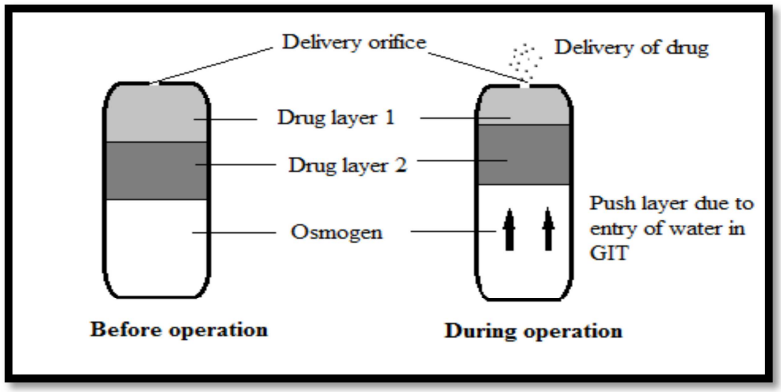

Figure 14: Multilayer osmotic pump

BASIC COMPONENTS OF OSMOTIC PUMPS

Drugs

Drug with biological half life > 12h e.g diazepam and drug which have very short half life i.e. <1h e.g. penicillin G, furosemide are not suitable candidate for osmotic controlled release. The drugs [57-61] having short biological half life(2-6h),prolonged treatment drugs e.g. nifedipine, glipizide, salbutamol, residronate sodium and highly potent drugs can be designed for osmotic drug delivery system.

Osmotic components/osmogents

Osmotic agents maintain a concentration gradient across the membrane. They create a driving force for the uptake of water and assist in maintaining drug uniformity in the hydrated formulation. Osmogents(Table 1) are used in the fabrication of osmotically controlled controlled drug delivery systems and modified devices for controlled release of relatively poorly water insoluble drugs. Osmogents generate osmotic pressure in the concentrated solution ranging from 8 atm to 500atm(Table2).

Classification of Osmogents [15]

Table1: **Compounds that can be used as osmogents**

Category	Examples
Water-soluble salts of inorganic acids osmogents	magnesium chloride or sulphate, sodium chloride, sodium sulphate,potassium chloride, sodium bicarbonate,sodium or potassium hydrogen phosphate etc.
Organic polymeric osmogents	sodium carboxy methylcellulose, hydroxyl propyl methyl cellulose,hydroxyl ethyl methylcellulose,methylcellulose,polyethylene oxide, polyvinyl pyrollidine,polyacrylamides,carbopols etc.
Carbohydrates	arabinose, ribose, xylose, glucose, fructose, galactose, mannose, sucrose, maltose, lactose, raffinose, etc
Water-soluble amino acids	glycine, leucine, alanine, méthionineds Glycine, leucine, alanine, méthionine, etc.
Water soluble salts of organic acids osmogents	sodium and potassium acetate,magnesium succinate,sodium benzoate,sodium citrate,sodium ascorbate etc.

Semipermeable membrane (SPM)

Semipermeable membrane is known as selectively permeable membrane or partially permeable membrane or differentially permeable membrane. SPM allows solvent and certain molecules or ions to pass through it by diffusion or specialized facilitated diffusion. The membrane is impermeable to the passage of drug and other ingredients present in the compartments. It should be inert and maintain its dimensional integrity to provide a constant osmotic pressure during the drug delivery[65].The selection of polymer is based on the solubility of drug as well as amount and rate of drug to be released from pump. The formation of SPM includes cellulosic polymers such as cellulose ethers, cellulose esters and cellulose ester-ether. The cellulosic polymers have a degree of substitution of 0 to 3 on the anhydroglucose unit. The degree of substitution is the number of hydroxyl groups present on the anhydroglucose unit replaced by a substituting group. The examples of these groups include cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate etc. The other SPM forming polymers are group consisting of acetaldehyde dimethyl cellulose acetate, cellulose acetate ethyl carbamate, cellulose dimethylamino acetate, polyamides, polyurethanes etc. The semi permeable membrane is generally 200-300µm thick to withstand the pressure within the device. The ideal properties of semi permeable membrane must have

sufficient wet strength, wet modulus, rigid dimensional integrity, water permeability, biocompatible, adequately thick to withstand the pressure generated within the device and the reflection coefficient and leakiness of the osmotic agent should approach the limiting value of unity. SPM selection of material is also depends on water vapor transmission rate. The water permeability to SPM is given in table no.3.

Table 2: Osmotic agents with their osmotic pressure [62-64]

S.No.	Osmogents	Osmotic pressure(atm)
1.	Adipic acid	8
2.	Fumaric acid	10
3.	Lactose	23
4.	Mannitol	38
5.	Potassium sulphate	39
6.	Tartaric acid	67
7.	Citric acid	69
8.	Dextrose	82
9.	Sorbitol	84
10.	Xylitol	104
11.	Potassium phosphate	105
12.	Melanic acid	117
13.	Sucrose	150
14.	Lactose-dextrose	225
15.	Potassium chloride	245
16.	Lactose-sucrose	250
17.	Fructose	355
18.	Mannitol-fructose	415
19.	Sucrose-fructose	430
20.	Dextrose-fructose	450
21.	Lactose-fructose	500
22.	Mannitol-dextrose	225
23.	Dextrose-sucrose	190
24.	Mannitol-sucrose	170
25.	Mannitol-lactose	130
26.	Sodium phosphate monobasicH_2O	28
27.	Sodium phosphate dibasic anhydride	29
28.	Sodium phosphate dibasic7H_2O	31
29.	Sodium phosphate dibasic12H_2O	31
30.	Sodium phosphate tribasic12 H_2O	36

Table 3:List of semi permeable membrane with their water vapor transmission rate(wvtr)[66]

S. No.	Polymer membrane	Wvtr(g/100m^2/24h/mmthick)
1.	Polyvinyl alcohol	100
2.	Polyurethane	30-150
3.	Methyl cellulose	70
4.	Cellulose acetate	40-75
5.	Ethyl cellulose	75
6.	Cellulose acetate butyrate	50
7.	Polyvinyl chloride(cast)	10-20
8.	Polyvinyl chloride(extruded)	6-15

Coating solvents

The primary function of solvent system is to dissolve or disperse the polymer and other additives and convey them to substrate surface. Coating solvents [67] are suitable for making polymeric solutions. It is used for manufacturing the wall of osmotic device and it should not harm the core and other excipients. It includes inert organic and inorganic solvents. The solvents used for coating solvents are methylene chloride, acetone, methanol, ethanol, isopropylalcohol, butyl alcohol, ethyl acetate, cyclohexane, carbon tetrachloride, water etc. The mixtures of solvents such as acetone-methanol(80:20), acetone-ethanol(80:20), acetone-water(90:10), methylene chloride-methanol(79:21), methylene chloride-methanol-water(75:22:3)etc.

Ideal properties of solvent system

(1) It should easily and completely dissolve polymer.

(2) It should easily disperse other coating components into solvent system.

(3) It should be odorless, colorless, tasteless, inexpensive, nontoxic and non irritant.
(4) It should have rapid drying rate.
(5) It should not give extremely viscous solution with small concentration of polymer(2-10%)

Emulsifying agents
The emulsifying agents act by regulating the surface energy of materials to improve their blending into the composite and maintain their integrity in the environment of use during the drug release period. Emulsifying agents[68] are useful when added to wall forming material to produce an integral composition to make the wall of the device. Emulsifying agents such as polyoxyethylenated glyceryl recinoleate, polyoxyethylenated castor oil having ethylene oxide, glyceryl laureates, glycerol(sorbitan oleate, stearateorlaurate) are incorporated into the formulation.

Flux regulating agents
Flux regulating or flux enhancing agent or flux decreasing agents are used in wall forming materials. It is added in the wall forming agents and it assists in regulating the fluid permeability of flux through wall. This agent [69] can be used to increase or decrease the liquid flux .The flux regulating agents may be hydrophilic substances and hydrophobic substances. The hydrophilic substances such as polyethylene glycols(300-6000D),polyhydric alcohols, polyalkylene glycols increase the flux whereas hydrophobic substances such as phthalates substituted with alkyl or alkoxy(diethyl phthalateordimethoxyethylphthalate) decrease the flux.

Wicking agents
Wicking agent is defined as a material with the ability to draw water into the porous network of delivery device. The wicking agent may be swellable or nonswellable in nature. They have the ability to undergo physisorption with water. Physisorption[70] is the form of absorption in which the solvent molecules can loosely adhere to surfaces of the wicking agent via vanderwaal's interactions between the surface of the wicking agent and the absorbed molecule. The function of wicking agent is to carry water to the surfaces inside the core of the device and creating channels or a network of increased surface area. Wicking agents such as colloidal silicon dioxide, kaolin, titanium dioxide, alumina, niacinamide, polyvinyl pyrrolidone, bentonite, sodium lauryl sulphate are incorporated into the formulation.

Plasticizers
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. Plasticizer enhances physical properties and improve film forming characteristics of polymers. It is used to lower the temperature in phase transition of the wall and also increase the workability, flexibility and permeability of the fluids. The ranges of plasticizer or mixture of plastizer between 0.01parts to 50 parts which is incorporated to 100parts of wall forming materials. Suitable solvents are used having high degree of solvent power for materials and compatible with the materials over both the processing and the temperature ranges to remain in the plasticized wall impart flexibility to the material[71]. Plasticizers such as phthalates(dibenzyl, dihexyl, butyl, octyl), triacetin, epoxidized tallate, triisoctyl trimellitate, alkyl adipates, citrates, acetates, propionates, glycolates, myristates, benzoates, halogenated phenyls are incorporated into the formulation.

Pore forming agents
These agents are particularly used in CPOP and multiparticulate osmotic pumps. The pore forming agents generate microporous[72] structure in the membrane due to its leaching during the operation of the system usually used for poorly water soluble drugs. The pores may be generated in the wall before operation of the system by gas formation by volatilization of components or by chemical reactions in polymer solution which creates pores in the wall. The pore formers can be inorganic and organic in nature. The examples of pore forming are alkaline metal salts such as sodium chloride,sodium bromide, potassium chloride, potassium sulphate, potassium phosphate etc., alkaline earth metals such as calcium chloride, calcium nitrate etc., carbohydrates such as sucrose, glucose. fructose, mannose, lactose, sobitol, mannitol, diols, polyols etc.

Barrier layer formers
The function of barrier former is to prevent water entry into certain parts of the delivery system and to separate the drug layer[73] from the osmotic layer. Barrier layer formers such as high density polyethylene, wax, rubber are incorporated into the formulation.

KEY PARAMETERS FOR DESIGNING OF OSMOTIC DRUG DELIVERY SYSTEMS

Drug delivery orifice size

Osmotic drug delivery systems consist of at least one delivery orifice in the SPM for drug release. The size of delivery orifice can be optimized in order to control the drug release from the osmotic systems. If the size of the delivery orifice is very small zero order delivery will be affected because of development of hydrostatic pressure within the core. The hydrostatic pressure is not relieved due to of small orifice size and may cause deformation of the delivery system resulting unpredictable drug delivery. Also the size of delivery orifice should not too large because solute diffusion from the orifice may take place. Hence to achieve an optimal zero order delivery profile the cross sectional area[74] of the orifice must be smaller than a maximum size Smax to minimum drug delivery by diffusion through orifice. The area is large above minimum size Smin to minimize the hydrostatic pressure build up in the system. Hence the cross sectional area of the orifice should be maintained between minimum and maximum values.

The minimum cross sectional area can be estimated from the following equation.

$$S_{min} = 5\left[(L/P_{max})\mu\right]^{1/2}(dv/dt) \text{.....(10)}$$

Where dv/dt is volume of flux through an orifice, L is length of the orifice (usually the same as thickness of the membrane),μ is viscosity of the drug solution flowing through the orifice and Pmax is maximum tolerated hydrostatic pressure difference across the membrane before occurrence of deformation of the housing The maximum cross sectional area of the orifice is obtained by specifying that the release rate must be smaller than a fraction f of the zero order pumping rates and is defined by following equation

.

$$S_{max} = \frac{M_{tz}\, f\, L}{DsCs} \text{.....(11)}$$

Where Mtz is the amount of the drug delivered in zero order fashion, and Ds is the drug diffusion coefficient in the permeating solvent. Some methods to create a delivery orifice in osmotic tablet coating are use of mechanical drill, laser drilling, use of modified punches, system with passageway formed in situ and use of pore former substances in the coating[75].

Laser drilling

In laser drilling process the top view of the portion of the apparatus utilized to drill hole in the osmotic tablets and the tablets in which holes are to be formed are charged in the hopper. The tablets drop by gravity into the slots of the rotating feed wheel and are carried at a predetermined velocity to the passageway forming station. At the passageway forming station each tablet is tracked by an optical tracking system. If the speed of the moving tablet increases the hole may become elliptical because of movement of tablets during the laser firing time. To avoid this problem tracking velocity is synchronized with the velocity at which the tablets are moving.The tracking is accomplished by the rotational oscillation of the mount and tracking mirror of the optical tracking system. During tracking laser beam is fired in a pulse mode in a pulse mode fashion and the beam is transmitted by the optical tracking mechanism onto the surface of the moving tablets and moves with the moving tablets as the mirror oscillates clockwise. The walls of the tablet absorb the energy of beam and gets heated ultimately causing piercing of the wall and thus forming passageway. After completion the tracking mirror oscillates anticlockwise back to its starting position to track the next tablet[76].It is possible to control the size of the passageway by varying the laser power, firing duration(pulse time),thickness of the wall and the dimensions of beam at the wall.

Systems with passageway formed in situ

The delivery passageway of oral osmotic systems is reported in US patent no.5736,159.The system comprises of a tablet core of the drug along with water swellable polymers and osmotic agents which is surrounded by rate controlling membrane. When it exposed to aqueous environment water is imbibed osmotically at a controlled rate and water swellable polymer expands as the osmotic agents dissolves and increases the osmotic pressure inside the tablet. This results in a rate controlled slight expansion of the partially hydrated core[77]. The expansion of core

causes a small opening to form at the edge of tablet from where the contents of the formulation are released. The nifedipine which is prepared by polyethylene oxide a water swellable agent releases the drug to plasma upto 24h in controlled manner.

Use of modified punches

The modified punches pierced the dosage form using a piercing device that is biased in a sheathed position and unsheathed upon application of compression force. The coating powder which to be compressed is charged to the die mold and an unpierced tablet core is placed upon it. Additional quantity of coating powder is added to the die mold subsequent to which both compression and piercing are done simultaneously**.** The another process for forming a passageway in osmotic system consists of charging the drug into round molds having a concave lower surface and compressing it with a plunger having a convex surface. After removing the plunger from the mold a second plunger equipped with a funnel shaped cone is pressed into the compressed drug thereby creating a small indention in the tablet core[78].

Use of pore formers

Inclusion of water soluble additives in the membrane wall is widely used for the development of CPOP system. These water soluble additives dissolve on when it comes contact with water leaving behind pores in the membrane through which drug release takes place. The release of drug from the system follows zero order kinetics and is independent of p^H . These pore formers or leachable materials produce one or more passageways with different geometrical shapes. The pores may be formed in the wall prior to the operation of the system by gas formation within curing polymer solutions, resulting voids and pores in the final form of the membrane [79].The pores of components in the polymer solution or by chemical evolution of gases prior to application or during application of the solution to the core tablets resulting in the creation of the polymer foams serving as the porous wall from where the drug release can take place.

Solubility

The kinetics of osmotic drug release is directly proportional to the solubility of the drug in the core of osmotic devices. Assuming osmotic device core contains pure drug ,the fraction of drug released from the core follows zero order kinetics. The release of drug from the device is expressed as the following equation.

$F_{(Z)}=1-S/\rho$……(12)

where $F_{(Z)}$is the fraction of drug released by zero order kinetics, S is the drug's solubility(g/cm^3) and ρ is the density(g/cm^3) of the osmotic system. The drugs having solubility of <0.05(g/cm^3) and density unity release the drug above 95% in the form of zero order kinetics. The zero order release rate is slow due to small osmotic gradient. But highly water soluble drugs demonstrate a high release rate of drugs that follows zero order kinetics for small percentage of initial drug load. It is possible to control the solubility of drugs within the core and extend the delivery of drugs for poor candidates for osmotic delivery. The drugs are designed for osmotic drug delivery have water solubility in the range 50-300mg/ml Some approaches are designed to deliver drugs having extremes of solubility are given below.

Use of wicking agents

Incorporation of wicking agents in osmotic formulations has been reported as an approach for poorly water soluble drugs. The agent is dispersed throughout the composition that increases the contact surface area of drug with the contact of aqueous fluids[80] e.g. colloidal silicon dioxide, sodium lauryl sulfate, etc. Hence the drug is released predominantly in a soluble form through the delivery orifice in the membrane.

Resin modulation approach

Incorporating positively charged anion exchange resin poly (4-vinyl pyridine) for the highly water soluble drug diltiazem hydrochloride is released from a CPOP modulated system. Hence ion-exchange resin approaches are commonly used to modify the solubility of drugs which alter the release of drug. Citric acid and adipic acids were used to maintain a low core p^H to assure that both the drug and resin carry positive charge. Pentaerythritol was used as osmotic agent and the release of diltiazem hydrochloride was in a controlled manner up to an extended period and follows p^H independent zero order release[81].

Use of swellable polymers

Swellable polymers were utilized for osmotic delivery of drugs having poor aqueous solubility of drugs. The formulation design comprises of a compartment containing the drug ,swelling agent and osmogents encapsulated with a rate controlling membrane. The examples of swelling agents are vinyl acetate copolymer, vinylpyrrolidone and polyethylene oxide. The drug is released at a constant rate due to uniform rate of swelling[82] of these polymers. The pressure produced during swelling is insufficient to rupture the system. PPOP type system delivers of high aqueous solubility drug e.g. oxybutynin chloride and low aqueous solubility drug e.g. glipizide in a controlled manner. The release of drug from the delivery orifice was in the form of fine dispersion. sandwiched osmotic tablets(SOTS) uses for osmotic delivery of water insoluble drugs such as nifedipine.

Use of effervescent mixtures

The effervescent mixture can be incorporated to deliver poorly water soluble drugs in the form of osmotic delivery system. When osmotic system is administered then the effervescent mixture containing the drug delivered under pressure through the delivery orifice in the membrane. Mixture of citric acid and sodium bicarbonate were used as effervescent couple for the delivery of aspirin. The formulation swells in water across the membrane causing the couple to generate an effervescent[83] solution that dispenses the drug in a suspension form.

Use of cyclodextrin derivatives

The cyclodextrin-drug complex is incorporated as an approach for delivery of poorly water soluble drugs from osmotic systems.In CPOP type of osmotic system testosterone solubility is increased by using cyclodextrin complex[84].The solubility of testosterone at 37^0C is 0.039mg/ml,and improved to 76.5mg/ml through complexation with sulfobutyl ether $^{\beta}$ cyclodextrin sodium salt,$(SBE)_{7m}{}^{\beta}$ -CD.

Use of alternative salt form

The change in salt form alters solubility[85]. It was reported in oxprenolol and metoprolol. It was observed that hydrochloride salt of oxprenolol was too soluble in water (70%w/v) making it difficult to maintain extended zero order delivery from osmotic dosage form. Hence it is substituted by less soluble succinate salt. In case metoprolol fumarate salt form is used instead of tartrate salt. The salt form was found to have optimum solubility and extended release up to 24h.

Use of encapsulated excipients

The encapsulated excipients mainly utilized in capsule device coated with asymmetric membranes to deliver drugs having poor water solubility. The poorly water soluble drug glipizide was improved by addition of encapsulated excipients(p^H controlling) within capsule device. Solubility modifier excipient [86] used in form of mini-tablet coated with rate controlling membrane to prolong its availability within the core. Thus the solubility of glipizide was improved and giving prolong release from device [87].

Use of crystal habit modifiers

Different crystal forms of drug has different aqueous solubility, it is beneficial to include a crystal modifying agent[88].Hence the excipients which may change crystal habit of drug can be used to modulate solubility. To slightly soluble drug carbamazepine by addition of crystal modifying agents (hydroxyl ethyl cellulose and hydroxyl methyl cellulose) and other excipients provides zero order drug release in the form of osmotic system.

Co-compression of drug with excipients

Inclusion of excipients modulate the solubility of drug within the core and control the release of the drug in osmotic systems. Different excipients[89] can be utilized to modulate the solubility of drugs with different mechanisms like saturation solubility, pH dependent solubility. McClelland et.al reported in CPOP of highly water soluble drug diltiazem hydrochloride(solubility more than 590mg/ml at 37^0C).The majority of drug fraction was released at first order rather than the zero order rate due to high water solubility. The solubility of diltiazem hydrochloride was reduced to 155mg/ml by addition of sodium chloride(at 1M concentration) into the core tablet formulation. The modification gave more than 75% of the drug to be released by zero order kinetics over a 14-16h period.

Use of lyotropic crystals

The lyotropic liquid crystals are non polymeric compounds molecular weight ranging from 200-1500D.It is also known amphipathic compounds. It forms mesophases which swells in presence of water[90].The examples of liquid lyotropic crystals are phosphatidyl choline(lecithin),phosphatidylethanolamine,phosphatidylserine,phosphatidyl

glycerol etc. Alcolec lecithin and mixture of soyabean phospholipids was used for osmotic delivery of two insoluble drugs such as glipizide and prazosin and giving extended drug release up to 24hr.

Osmotic pressure

It is necessary to keep constant osmotic pressure[91] by maintaining a saturated solute solution to achieve zero order release rate. The osmotic pressure gained by the saturated drug solution is not sufficient to achieve the required driving force. Hence osmotic agents are incorporated to generate osmotic pressure inside the device.

Semipermeable membrane

The SPM is permeable to water and not to ions. Hence the release rate is independent of the pH of the environment. The SPM should stable both the outer environment and inner environment of the device [92].

ADVANTAGES OF OSMOTIC DRUG DELIVERY SYSTEM [93,94]

(1)The release of drugs follows zero order kinetics after an initial lag.
(2)The delivery of drug may be delayed or pulsatile.
(3)The drug release is independent of of gastric P^H,drug and in hydrodynamic condition.
(4)The drug delivery provides high degree of in vitro in vivo correlation.
(5)The drug release is higher than conventional drug delivery system.
(6)The release of drug is less affected by the presence of food in gastrointestinal tract.

DISADVANTAGES OF OSMOTIC DRUG DELIVERY SYSTEM[95]

(1)The method of preparation is very costly.
(2)The making of hole in semi permeable is very difficult.
(3)There is a chance of dose dumping if the coating process is not well controlled

MARKETED PRODUCTS

Many osmotic drug delivery system products are available in market which is shown in Table 4.

Table 4: Some marketed products of osmotic drug delivery systems

S.No.	Product name	Active pharmaceutical ingredients	Design of osmotic pump	Developer/Marketer	Ref. No.
1.	Acutrim	Phenylpropanolamine	EOP	Alza/Heritage	15
2.	AlpressLP	Prazosin	PPOP	Alza/Pfizer	18
3.	CarduraXL	Doxazosin	PPOP	Alza/Pfizer	96
4.	CoveraHS	Verapamil	PPOPwithtimedelay	Alza/GD Searle	97
5.	DitropanXL	Oxybutinin chloride	PPOP	Alza/UCB Pharma	15
6.	Dynacire CR	Isradipine	PPOP	Alza/Novartis	96
7.	Efidac24	Pseudoephiderine	EOP	Alza/Novartis	98
8.	Glucotrol XL	Glipizide	PPOP	Alza/Pfizer	99
9.	MinipressXL	Prazosin	PPOP	Alza/Pfizer	36
10.	ProcadiaXL	Nifedipine	PPOP	Alza/Pfizer	97
11.	Sudefed24h	Pseudoephidrine	PPOP	Alza/WarnerLambert	36
12.	Teczam	EnalprilandDiltiazem	EOP	Merck/Aventis	100
13.	Tiamate	Diltiazem	PPOP	Merck/Aventis	100
14.	Volmax	Albuterol	PPOP	Alza/Muro	101

PATENTS ON OSMOTIC DRUG DELIVERY SYSTEM

Table 5: Patents on osmotic drug delivery system
In recent years many osmotic drug delivery systems patents are available(Table 5).

Sl.no	Patent no.	Title	Publication date	Inventors	Ref.no.
1.	US3977404	Osmotic device having microporous reservoir	Aug.31,1976	Felix Theeuwes	102
2.	US4285987	Osmotic system for dispensing drugs	Aug.25,1981	Atul.D.Ayer,F.Theeuwes	103
3.	EP0169105	Controlled porosity osmotic pump	Jan.22,1986	Gaylen M.Zentner,Gerald S.Rork,Kenneth J.Himmnelstein	104
4.	US4946686	Solubility modulated drug delivery system	Aug.7,1990	Gregory A. Mccelland,Gaylen M.Zentner	105
5.	EP0309051	Controlled porosity osmotic pump	Mar.11,1992	John L.Haslam,Gerald S.Rork	106
6.	WO1994001093	Controlled porosity osmotic enalpril pump	Jan.20,1994	John L.Haslam,Gerald S.Rork	107
7.	US5672167	Controlled release osmotic pump	Sept.30,1997	Amulya L.Athayde,Rolf A.Faste,C.Russell Horres Jr,Thomas P.Low	108
8.	WO2001032149	Osmotic controlled release drug delivery device	May 10,2001	Laura A Debusi,Stephen B Ruddy,David E Storey	109
9.	US8109923	Osmotic pump with remotely controlled pressure generation	Feb.7,2012	LE Hood,MY Ishikawa,EKY Jung,R Langer,T Clarence,TLL Wood,VYH Wood	110

CONCLUSION

Osmotic drug delivery systems utilize the principle of osmotic pressure for drug delivery system. The drug delivery from osmotic system is independent of the physiological factors of gastrointestinal tract. By optimizing various formulation factors such as solubility, osmotic pressure of core components, size of delivery orifice and nature of rate controlling membrane the drug delivery can be controlled. The release of drug follows zero order kinetics and more safer than conventional dosage forms.

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