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A COMPREHENSIVE REVIEW ON OSMOTICALLY CONTROLLED ORAL DEVICE

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Keywords:

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ABSTRACT: The most well-known widely used route of administration among all the routes that have been explored for the systemic delivery of drugs is oral drug delivery. Drugs can be delivered in a controlled pattern over a long period of time by the controlled or modified release drug delivery systems. The osmotic-controlled release oral delivery system, OROS, is an advanced drug delivery technology that uses osmotic pressure as the driving force to provide pharmacotherapy, usually once daily, in several therapeutic areas. This system is independent of the physiological factors of the gastrointestinal tract and can be utilized for systemic as well as targeted delivery of drugs. Osmotic pumps consist of a core coated with a semi-permeable membrane. As the core absorbs water, it expands in volume, which pushes the drug solution out through the delivery ports. It mostly consists of three things a semi-permeable membrane, a core, and a delivery orifice. This paper highlights the principle of osmosis, materials used for the fabrication of pumps, types of pumps, advantages, disadvantages, and marketed products of this system. This review brings out new technologies, fabrication, and recent clinical research in osmotic drug delivery. Overall, oral osmotically driven systems appear to be a promising technology for product life-cycle strategies.

INTRODUCTION: Conventional oral drug delivery systems are known to provide an immediate release of the drug where drug release cannot be controlled and cannot maintain effective concentration at the target site for a longer period of time. An osmotically controlled drug delivery system delivers the drug to a large extent, and the delivery nature is independent of the physiological factors of the gastrointestinal tract, and these systems can be utilized for systemic as well as targeted delivery of drugs. The osmotic drug delivery system releases drugs with zero-order kinetics at a constant rate for 24 h, which does not depend on initial concentration.

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The speed of drug release from the osmotic pump is directly proportional to the osmotic pressure developed due to imbibitions of fluids by osmogens. Once the tablet comes in contact with the aqueous environment, the water-soluble component dissolves, water diffuses into the core through the microporous membrane, setting up an osmotic gradient and thereby controlling the release of drug [1, 2]. 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 semi-permeable membrane, which is permeable only to the solvent and impermeable to the solute.

The pressure applied to the higher-concentration side to inhibit solvent flow is called the osmotic pressure. Osmotic drug-delivery systems suitable for oral administration typically consist of a compressed tablet core that is coated with a semi-permeable membrane coating. This coating has one or more delivery ports through which a solution or

suspension of the drug is released over time. The core consists of a drug formulation that contains an osmotic agent and water-swellable polymer. The rate at which the core absorbs water depends on the osmotic pressure generated by the core components and the permeability of the membrane coating.

As the core absorbs water, it expands in volume, which pushes the drug solution or suspension out of the tablet through one or more delivery ports [2]. The historical development of osmotic systems includes seminal contributions such as the Rose–Nelson pump, the Higuchi Leeper pumps, the AlzetR and OsmetR systems, the elementary osmotic pump, and the push-pull system.

Recent advances include the development of the controlled porosity osmotic pump systems based on asymmetric membranes and other approaches. One advanced drug delivery technology, OROS technology (Alza Pharmaceuticals, Palo Alto, California) relies on the principle of osmosis as the driving force for controlled drug release. Drug release from osmotic systems is generally unaffected by the body's pH, presence of food, or other physiological factors.

OROS technology is designed to modulate and release a drug at a controlled rate over an extended period. OROS technology has evolved through the years, from the original elementary osmotic pump to the push-pull system and, subsequently, the advanced longitudinally compressed tablet (LCT) multilayer formulation [2, 3].

Advantages of Osmotic Drug Delivery Systems: Osmotic drug delivery systems for oral and parenteral use offer distinct and practical advantages over other means of delivery. Osmotic drug delivery systems have advantages such as [3, 4, 5]

1. They typically give a zero-order release summary after an initial lag.
2. Delayed or pulsed delivery.
3. Drug discharge is free of gastric pH and hydrodynamic state.
4. They are well unspoken and characterized.
5. The release mechanisms are not dependent on the drug.
6. A high quantity of in-vitro and in-vivo correlation (IVIVC) is obtained in osmotic systems.
7. 7Superior release rates are promising with osmotic systems compared with predictable diffused controlled drug delivery systems.
8. The release from osmotic systems is generally unaffected by the presence of food in the gastro intestinal tract.

Limitations of Osmotic Drug Delivery Systems: [3, 4, 5]

- Special equipment is necessary for making an orifice in the system.
- It may cause irritation or ulcer due to the release of a soaking solution of the drug.
- Dose dumping.
- Retrieval therapy is not possible in the case of unpredicted adverse events.
- Luxurious.
- If the coating process is not well controlled, there is a danger of film defects, which outcome in dose is discarding.
- Orifice size is critical.

The Rose Nelson Pump: In 1955, two Australian physiologists Rose and Nelson, reported the first osmotic pump. They have observed the delivery of drugs to the gut of sheep and cattle. The osmotic pump consists of:

- A drug chamber with an orifice.
- A salt chamber with elastic diaphragm containning excess solid salt.
- A water chamber.

The drug and water chamber are separated by a rigid semi-permeable membrane. The difference in osmotic pressure across the membrane moves water from the water chamber into the salt chamber.

The volume of the salt chamber increases because of this water flow, which distends the latex diaphragm separating the salt and drug chamber, thereby pumping drug out of this device [6, 7].

TABLE 1: HISTORICAL ASPECTS OF OSMOTIC PUMPS: [6]

Year	Comments/Inventions
1748	First report of osmosis
1877	Quantitative measurement of osmotic pressure
1955	First osmotic pump by rose and nelson
1973	Higuchi Leeper introduced a new version of the rose and nelson pump with certain modification Osmotically powdered agent dispense device with filling means
1975	Major milestones in the field of osmotic drug delivery system introduced the first oral Osmotic i.e. elementary osmotic pump
1976	Patent grand on the design of the osmotic pump
1981	Effervescent activity-based system introduced
1982	Volume amplifier devices introduced Patent issues for an osmotic system which consist of layer swellable hydrogel
1984	First report on combination therapy by push-pull osmotic pump
1985	Controlled pump osmotic pump developed
1986	Patent issues claim a delivery for controlled administration of the drug to ruminants
1989	Developed push-pull osmotic pump for nifedipine by Pfizer
1994	Pulsatile delivery based on expandable orifice
1999	Patent to an osmotic dosage form for liquid drug delivery
1999	Asymmetric membrane capsule introduced
2000	Durosleurpolid implants that is, verdure approved as first implantable osmotic pump for human by USFDA
2001	Patent granted for dosage form comprising liquid drug formulation that can self-emulsify to enhance the solubility, dissolution, and bioavailability of drug
2003	First report floating osmotic system

About 75 years after the discovery of the osmosis principle, it was first used in the design of drug delivery systems.

Higuchi Leeper Pump: The Higuchi Leeper pump represents the better version of the Rose Nelson pump made by the Alza Corporation in early 1970. The benefit of this pump over the Rose Nelson pump is that it does not have a water chamber, and the device is activated by water imbibed from the surrounding environment, which means the pump is first prepared and then loaded with the drug and then it is stored for weeks and months.

Higuchi Theeuwes Pump: In the early 1970, Higuchi Theeuwes developed a similar form of Rose Nelson pump. The semi-permeable wall itself acts as a rigid outer casing of the pump. The device is loaded with the drug prior to use. When the device comes in contact with the aqueous environment, the release of the drug follows a time course set by the salt used in the salt chamber and the permeability of the outer membrane casing.

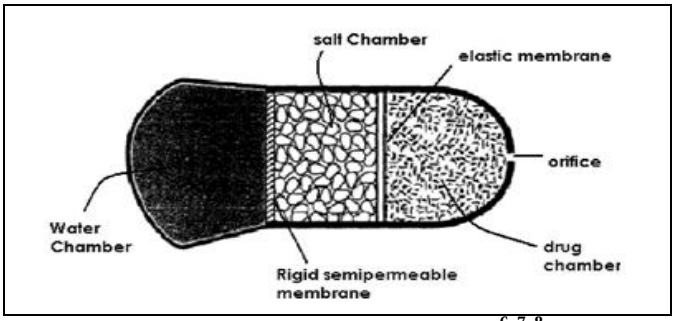

FIG. 1: ROSE NELSON PUMP [6, 7, 8]

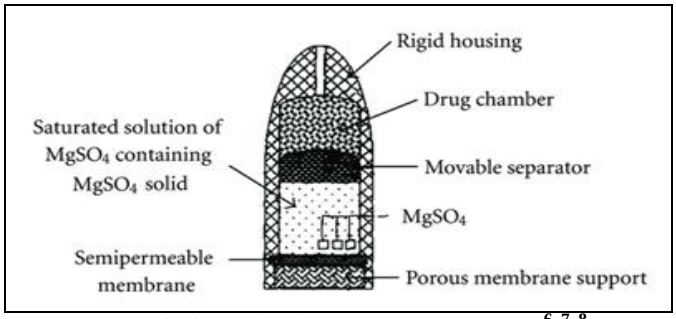

FIG. 2: HIGUCHI LEEPER PUMP [6, 7, 8]

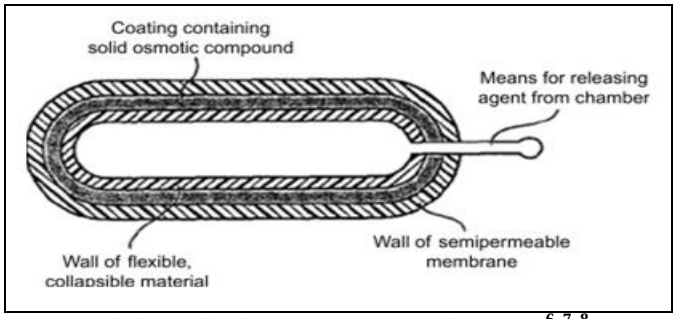

FIG. 3: HIGUCHI- THEEUWES PUMP [6, 7, 8]

Basic Components of Osmotic Systems [8, 9, 10]

Drugs: Drugs must have a short biological half-life, which is used for prolonged treatment. The basic Criterion for Drug Selection:

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

Various drug candidates such as Diltiazem HCl, Carbamazepine, Metoprolol, Oxprenolol, Nifedipine, Glipizideetc are formulated and marketed as osmotic delivery.

Osmotic Agents: Osmotic agents maintain a concentration gradient across the membrane. They also generate a driving force for the uptake of water and assist in maintaining drug uniformity in the hydrating formulation. 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. 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 carboxy-polymer), Cyanamer (Polyacrylamides), and Aqua-Keeps (acrylate polymer polysaccharides composed of condensed glucose units such as diester cross-linked polygluran) may be used to achieve optimum osmotic pressure inside the system.

Wicking Agents: Wicking agents are defined as material with the ability to draw water into the porous network of delivery system devices. The wicking agent helps to increase the contact surface area of the drug with the aqueous fluid. They may be either swellable as well as non-swellable in nature. A physisorption is a form of absorption in which the solvent molecules can loosely adhere to the surface of a wicking agent with vader wall's interactions between the surface of the wicking agent and adsorbed molecule.

The function of wicking agents is to carry water to the surface inside the core of the tablet, which helps in creating channels or a network of increased surface area. Example: - colloidal silicon dioxide, kaolin, titanium dioxide, alumina, sodium lauryl sulphate, *etc.*

Semi-permeable Membrane: An important part of the osmotic drug delivery system is the semi-permeable membrane in which polymeric membrane got selected. 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.

Flux Regulators: Delivery systems can be designed to regulate the permeability of the fluid by incorporating flux regulating agents in the layer. Hydrophilic substances such as polyethylene glycols, polyhydric alcohols, and polyalkylene glycols improve the flux, whereas hydrophobic materials such as phthalates are 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, can also be used for this purpose

Coating Solvents: Solvents are defined as the polymeric solution used in the manufacturing of the walls of osmotic devices, includes inert inorganic and organic solvents that do not adversely harm the core wall and other material. For example, methylenechloride, acetone, methanol, ethanol, isopropylalcohol, butylalcohol, ethylalcohol, *etc.*

Hydrophilic and Hydrophobic Polymers: These polymers are used in the formulation development of osmotic systems for making drug-containing matrix core. The selection is based on the solubility of the drug as well as the amount and rate of drug to be released from the pump. The polymers are of either swellable or non-swell able nature. Mostly, swell able polymers are used for the pumps containing moderately water-soluble drugs, since they increase the hydrostatic pressure inside the pump due to their swelling nature. The non-swell able polymers are used in case of highly water-soluble drugs. Ionic hydrogels such as sodium carboxymethyl cellulose are preferably used because of their osmogenic nature.

Surfactants: Surfactants are particularly useful when added to wall-forming material. They produce an integral composite that is useful for making the wall of the device operative. The surfactants 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. Typical surfactants such as poly oxyethyl-enatedglycerylrecinoleate, polyoxyethylenated castor oil having ethylene oxide, glyceryl laurates, and glycerol (sorbitonoleate, stearate, or laurate) are incorporated into the formulation.

Pore Forming Agents: These agents are particularly used in the pumps developed for poorly water-soluble drugs and in the development of controlled porosity or multiparticulate osmotic pumps. 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, *etc*., alkaline earth metals such as calcium chloride and calcium nitrate, carbohydrates such as sucrose, glucose, fructose, mannose, lactose, and polyols such as polyhydric alcohols and polyvinyl pyrrolidone can also be used.

Plasticizers: In pharmaceutical coatings, plas-ticizers or low molecular weight diluents are added to modify the physical properties and improve film-forming characteristics of polymers. Plasticizers can change the viscoelastic behavior of polymers significantly. They can turn a hard and brittle polymer into a softer, more pliable material, and possibly make it more resistant to mechanical stress.

They also lower the temperature of the second order-phase transition of the wall or the elastic modulus of the wall and also increase the workability, flexibility, and permeability of the coating solvents. PEG-600, PEG-200, triacetin (TA), dibutylsebacate, ethylene glycolmono acetate, ethylene glycol diacetate, triethyl phosphate, and diethyl tartrate used as a plasticizer in the formulation of Semipermeable membrane.

Factors Influencing the Design of Osmotic Controlled Drug Delivery Systems: [9, 10, 11, 12]

Drug Solubility: For the osmotic system, the solubility of the drug is one of the most important parameters affecting drug release kinetics from osmotic pumps.

The kinetics of osmotic drug release is directly related to the drug solubility within the drug core. Drugs with a density of unity and the solubility of $\leq$ 0.05 g/cm^3 would be released with $\geq$ 95% zero-order kinetics. At the same time, highly water-soluble drugs would demonstrate a high release rate that would be zero-order for a small percentage of the initial drug load. Thus, the intrinsic water solubility of many drugs might prohibit them from incorporation into an osmotic pump. Candidate drugs for osmotic delivery have water solubility in the range 50-300 mg/ml.

Some of the Approaches that have been used to Change the Drug Solubility within the Core Include:

- Co-compression of the drug with excipients, which change the drug's solubility within the core.
- Use of fizzy mixtures to speed up the release of poorly soluble drugs from the orifice.
- Use of various cyclodextrin derivatives to solubilize poorly water-soluble drugs.
- Use of substitute salt form that has the best possible water solubility.
- Use of encapsulated excipients.
- Use of lyotropic crystals.
- Use of wicking agents.

Membrane Thickness: One of the important factors which control the rate of penetration of water into the device is the thickness of the membrane. The permeability of water into the membrane can be enhanced by choice of a suitable type of membrane material. The time of release of the active constituent can be easily varied by as much as 1000 fold based upon the thickness of the membrane. In general, the rate of drug release can be achieved by varying the membrane material, while small change up to a five percent can be best

achieved by varying the thickness of the membrane.

Orifice Size: To achieve an optimal zero-order delivery profile, the cross-sectional area of the orifice must be smaller than a maximum size to minimize drug delivery by diffusion through the orifice.

Furthermore, the area must be sufficiently large above a minimum size to minimize hydrostatic pressure buildup in the system. Otherwise, the hydrostatic pressure can deform the membrane and affect the zero-order delivery rate.

Semi-Permeable Membrane: Some of the membrane variables that are significant in the device of oral osmotic system are: Cellulose acetate, cellulose dilacerate, cellulose triacetate, cellulose propionate, cellulose acetate butyrate, ethylcellulose, and eudragits.

Osmotic Pressure: The osmotic pressure directly affects the release rate. To achieve a zero-order release rate, it is essential to keep osmotic pressure constant by maintaining a saturated solute solution.

Mostly 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.

Type and Amount of Plasticizer: In pharmaceutical coatings, low molecular weight diluents are added to change the physical properties and get better film-forming individuality of polymers. In particular, plasticizers can turn a hard and fragile polymer into a softer, more flexible material and possibly make it more resistant to automatic stress. These changes also affect the permeability of polymer films.

Classification of Osmotic Drug Delivery Systems: [12-18] The osmotically controlled oral drug delivery system can be conveniently classified in to following types:

Single Chamber Osmotic Pump:

1. Elementary osmotic pump.

Multi-Chamber Osmotic Pump:

1. Push-pull osmotic pump
2. Osmotic pump with non-expanding second chamber.

Specific Types of Osmotic Pumps:

- Controlled porosity osmotic pump
- Osmotic bursting osmotic pump
- Liquid OROS
- Delayed delivery osmotic device
- Telescopic capsule
- Oros-Ct
- Sandwiched osmotic pump
- Osmotic pump for insoluble drugs
- Monolithic osmotic systems

Single Chamber Osmotic Device: [12, 13]

Elementary Osmotic Device: The elementary osmotic device was introduced in the 1970s to deliver the drug at zero-order rates for a prolonged period and is minimally affected by environmental factors such as pH or motility. The EOP consist of a single-layered tablet core containing a water-soluble drug with or without other osmotic agent surrounded by the semi-permeable membrane. When the tablet is swallowed, water from the GIT enters through the membrane in the core, the drug dissolved, and the drug solution is pumped out through the exit orifice. This process continues at a constant rate until the entire solid drug inside the tablet has been dissolved, and then it is delivered at a declining rate until the osmotic pressure between outside and inside the environment gets saturated. Normally the EOP delivers 60-80% of its content at a constant rate, and there is a short lag time of 30-60 min as the system hydrates before zero-order drug release from the EOP is obtained. The disadvantages of the elementary pump are that it is only suitable for the delivery of water-soluble drugs.

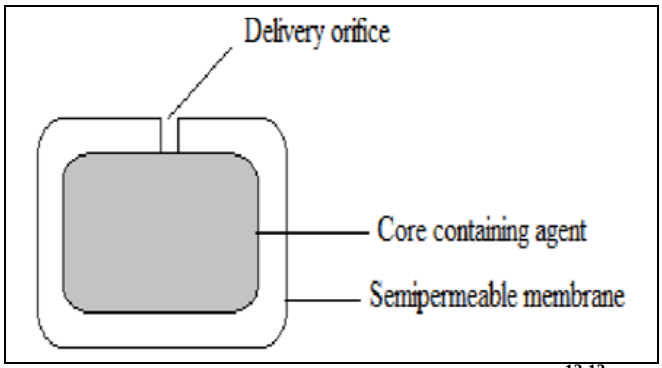

FIG. 4: ELEMENTARY OSMOTIC PUMP [12-13]

Multi-Chamber Osmotic Device: [12, 13]

Push and Pull Osmotic Device: Push and pull osmotic device is the modified version of the elementary osmotic device, and in this, it is possible to deliver both poorly water-soluble and highly water-soluble drugs at a constant rate. It resembles a standard bilayer coated tablet one layer (depict as an upper layer) contains the drug in the formulation of polymeric osmotic agent and other tablet excipients. These layers are formed separately and bonded together by tablet compression to form a single bilayer core. The tablet core is then coated with a semi-permeable membrane. After the coating is applied, a small hole is drilled through the membrane by a laser or mechanical drill of the drug layer side of the tablet. When the system is placed in an aqueous environment, water is imbibed into the tablet by an osmotic agent within the layers. Osmotic agent in non-drug layer simultaneously attract water into the compartment, causing it to expand volumetrically and the expansion of non-drug layer push the drug suspension out of the orifice and is also known as an expandable osmotic device.

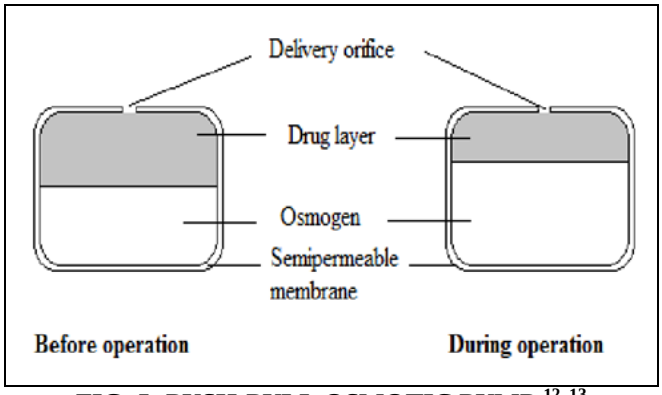

FIG. 5: PUSH-PULL OSMOTIC PUMP [12, 13]

Osmotic Device with Non-Expanding Second Chamber: [12, 13] The second category of multi-chamber devices comprises a system containing a non-expanding second chamber. In one category of these devices, the second chamber is used to dilute the drug solution leaving the devices. Water is also drawn osmotically into this chamber either because of the osmotic pressure of the drug solution or because the second chamber contains water-soluble diluents such as NaCl.

This type of devices consists of two rigid chambers, the first chamber contains a biologically inert osmotic agent, such as sugar or a simple salt like sodium chloride, and the second chamber contains the drug. When water is drawn into both the chamber through the surrounding semi-permeable membrane, the solution of osmotic agent 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 microporous membrane that forms a part of the wall surrounding the chamber. The device could be used to deliver relatively insoluble drugs.

Controlled Porosity Osmotic Device: [13, 14] A controlled porosity osmotic pump (CPOP) drug delivery system, unlike the elementary osmotic pump (EOP), which consists of an osmotic core with the drug surrounded by a semi-permeable membrane drilled with a delivery orifice, controlled porosity of the membrane is achieved by the use of different channeling agents in the coating. The CPOP contains water-soluble additives in the coating membrane, which after coming in contact with water, get dissolves resulting in an in-situ formation of a microporous membrane. Then the resulting membrane is significantly permeable to both water and dissolved solutes, and the mechanism of drug release from the system was found to be primarily osmotic with simple diffusion. Drug delivery from asymmetric membrane capsule is principally controlled by the osmotic pressure of the core formation. In-situ formed delivery orifice in the asymmetric membrane is mainly responsible for the solubilization in the core for a drug with poor water solubility.

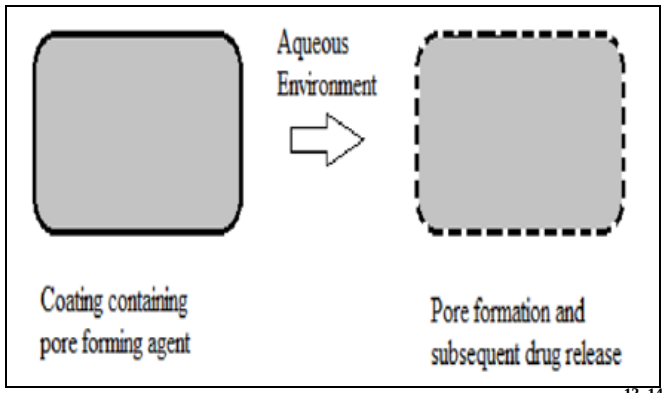

FIG. 6: CONTROLLED POROSITY OSMOTIC PUMP [13, 14]

Multiparticulate Delayed Release System: [14, 15] MPDRS consists of pellets comprises of drugs with or without an osmotic agent, which are coated with a semi-permeable membrane. When this system

comes in contact with the aqueous environment, water penetrates the core and forms a saturated solution of the soluble component. The osmotic pressure difference results in the rapid expansion of the membrane, leading to the formation of pores. The osmotic agent and the drug released through the pores according to zero-order kinetics. The lag time and dissolution rate were found to be dependent on the coating level and the osmotic properties of the dissolution medium.

Monolithic Osmotic Device: [15, 16] It consists of a simple dispersion of water-soluble agents in a polymer matrix. When the system comes in contact with the aqueous environment water imbibitions by the active agents take place rupturing the polymer matrix capsule surrounding the drug, thus liberating it to the outside environment. Initially, this process occurs at the outer environment of the polymeric matrix but gradually proceeds towards the interior of the matrix in a serial fashion. However, this system fails if more than 20-30 volume per liter of the active agents is incorporated into the device as above this level, a significant contribution from the simple leaching of the substance takes place.

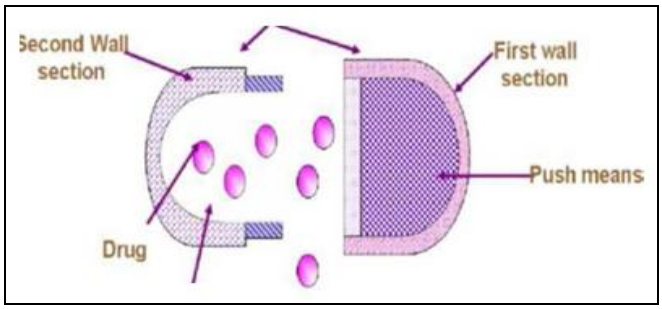

FIG. 7: MULTI-PARTICULATE DELAYED RELEASESYSTE [14, 15]

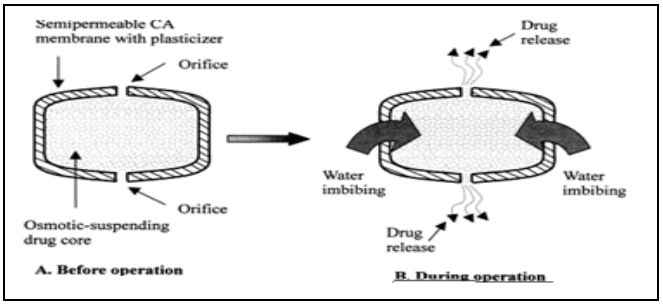

FIG. 8: MONOLITHIC OSMOTIC DEVICE [15, 16]

Osmotic Bursting Osmotic Devices: This system is similar to an EOP expect the delivery orifice is absent, and size may be smaller. When it is placed in an aqueous environment, water is imbibed, and hydraulic pressure will generate until the wall rupture and the content are released to the environment. The thickness, as well as the area of semi permeable membrane, can control the release of the drug. This system is useful to provide pulsated release [15, 16].

OROS-CT: OROS-CT is used as a once or twice a day formulation for targeted delivery of drugs to the colon. The OROS-CT can be a single osmotic agent or it can be comprised of as many as five to six push pull osmotic unit filled in a hard gelatin capsule. After coming in contact with the GIT fluid gelatin capsule dissolve and the enteric coating prevents entry of fluids from stomach to the system as the system enters into the small intestine the enteric coating dissolves and water is imbibed into the core thereby causing the push compartment to swell. At the same time flowable gel is formed in the drug compartment, which is pushed out of the orifice at a rate, which is precisely controlled, by the rate of water transport across the semi permeable membrane [15, 16].

Liquid Oral Osmotic System (L-Oros): Various LOROS systems available to provide controlled delivery of liquid drug formulations which includes L-OROS hard cap, L-OROS soft cap and a delayed liquid bolus delivery system. Each of these systems includes a liquid drug layer, an osmotic engine or push layer, and Semi-permeable membrane coating.

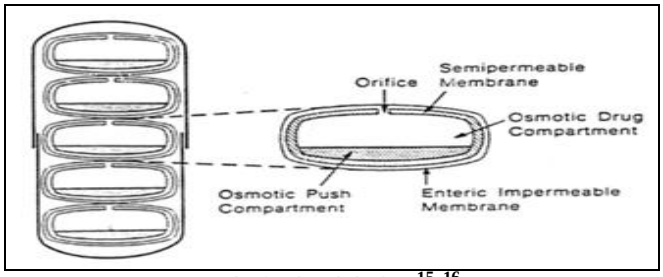

FIG. 9: OROS-CT [15, 16]

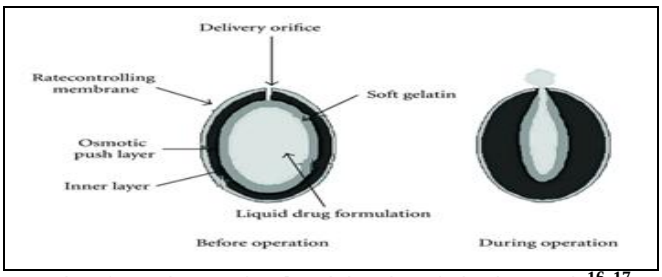

FIG. 10: LIQUID ORAL OSMOTIC SYSTEMS [16, 17]

When the system is in contact with the aqueous environment, water permeates across the rate-controlling membrane and activates the osmotic layer. The expansion of the osmotic layer results in the development of hydrostatic pressure inside the system, thereby forcing the liquid formulation to be delivered at the delivery orifice. In contrast, system comprises three layers: a placebo delay layer, a liquid drug layer, and an osmotic engine, all surrounded by a rate-controlling Semi-permeable membrane (SPM). The delivery orifice is drilled on the placebo layer end of the capsule-shaped device. When the osmotic engine expands, the placebo is released first, delaying the release of the drug layer. Drug release can be delayed from 1 to 10 h, depending on the permeability of the rate-controlling membrane and the size of placebo [16, 17].

Sandwiched Osmotic Tablet: In this type of tablet core of the tablet, composed of a polymeric push layer sandwiched between two drug layers with two delivery orifices. When placed in an aqueous environment, the middle push layer containing swelling agent swells and dug is released from two orifices situated on opposite sides of the tablet, and a sandwiched osmotic device can be utilized for drug prone to cause local irritation for gastric mucosa [16, 17].

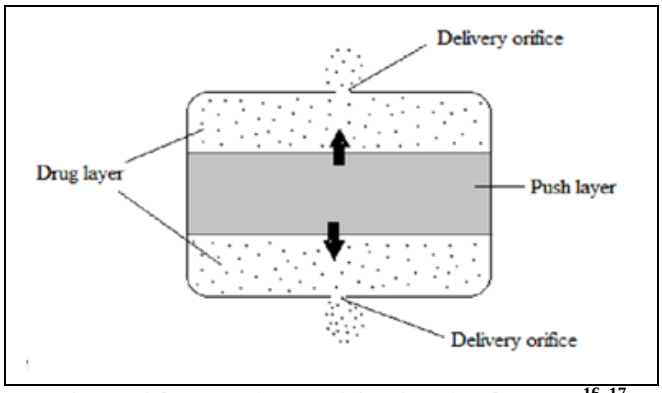

FIG. 11: SANDWICHED OSMOTIC TABLET [16, 17]

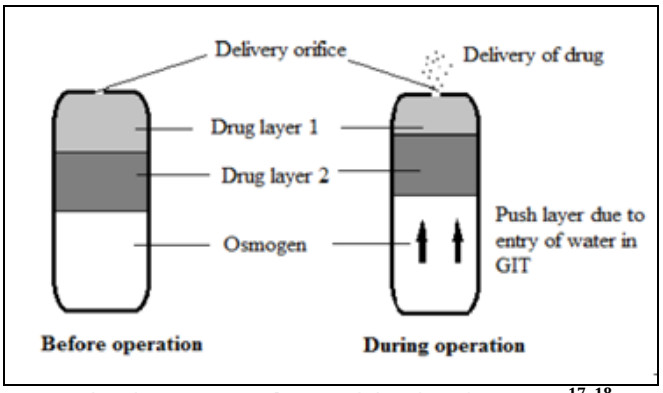

FIG. 12: MULTILAYER OSMOTIC PUMP [17, 18]

Longitudinally Compressed Tablet Multilayer Formulation: The LCT multilayer formulation is the advanced design. As with the push-pull system, it consists of an osmotic push layer and can be configured to contain several drug layers. The opinion of multiple drug layers provides increased flexibility and control over the pattern of release of medication from the system, as opposed to the single-layer used in the push-pull system, which can deliver a drug only in a zero-order rate.

As with the push-pull formulation, water is absorbed through the exposed Semi-permeable tablet shell, expanding the push compartment and releasing the drug primarily through the first compartment through the laser-drilled orifice at a predetermined controlled rate. After most of the drug, release begins from the second compartment at a different rate. This allows even greater flexibility to achieve the target release profile. The LCT multilayer formulation can also be formulated with different drugs in different layers to provide a combination therapy. Similar to the push-pull system, drug delivery by the LCT multilayer formulation can be unaffected by gastric pH, gut motility, and the presence of food, depending on where in the GI tract the drug is released [17, 18].

Telescopic Capsule for Delay Release: It consists of two chambers, first containing the drug, and the exit port second contains an osmotic agent. A layer o-wax like material separates these two sections. To assemble the delivery system, the desired active agent is placed into one of the sections by manual or automated fill mechanism. The bilayer tablet with the osmotic agent part is placed into the cap part of the capsule with a convex osmotic layer pointed into the closed end of the cap and the barrier layer exposed towards the cap opening. The open end of the filled vessel is fitted inside the open end of the cap, and two pieces are compressed together until the cap, osmotic bilayer tablet and vessel fit together tightly. As the fluid is imbibed in the device, the osmotic agent part expands and exerts pressure on the first and second wall section. As the result the net flow of fluid driven by pressure enters the reservoir is minimal and consequently, no agent is delivered for a period [17, 18].

Lipid Osmotic Device: The pump concerns an osmotic agent, which is mainly used for the drug having poor solubility in water. The core of the system comprises a water-insoluble agent, which is lipid-soluble, a sufficient amount of water-insoluble lipid carrier, which is used to dissolve or suspend the drug and agent to ensure the release of lipid carrier of the drug from the device. The water-insoluble wall is microporous and is wetted by lipid carrier. The device is prepared by dissolving the drug of interest in a lipid vehicle. The osmogens sodium chloride is dispersed in the melted liquid and the quenched cool to form a lump that is broken and made in to tablet. The microporous is coated at moderate flow of unheated ambient [17, 18].

Pulsatile Drug Delivery System: The principle rationale for the use of pulsatile release is for the drugs where a drug does not constantly release *i.e.*, zero-order release is not desired. The release of drug as pulse after a lag time has to be designed in such a way that a complete and rapid drug release follows lag time. The types of tablet systems consist of core coated with two layers of swelling and rupturable coating in which they used spray-dried lactose and microcrystalline cellulose in drug core that was coated with swelling polymer croscarmellose sodium and an outer rupturable layer of ethyl cellulose. The pulsatile system can be classified into a single and multiple-unit system. Single unit systems are formulated either as a capsule-based or osmosis based system. These are designed by coating the system either with erodible or soluble or rupturable coating. In a multiple-unit system, however, the pulsatile release is induced by changing membrane permeability or by coating with rupturable membrane [17, 18].

Review on Work Done:

Gregory A. McClelland 1991: Investigated the application of solubility- or resin-modulation methods in which the drug releases kinetics from controlled porosity osmotic pumps have been effectively manipulated. The solubility of diltiazem hydrochloride was modulated for an extended period of 12-14 h through the incorporation of controlled release sodium chloride elements into the core tablet formulations. *In-vitro* diltiazem hydrochloride release profiles were zero-order, and pH-independent were obtained without chemical modification of the drug in both the examples. With similar *in-vivo* and *in-vitro* kinetics, the solubility-modulated devices adminis-tered to dogs released diltiazem hydrochloride [19].

Hai Bang Leeb 2000: Described the monolithic osmotic tablet system composed of a monolithic tablet coated with cellulose acetate (CA) membrane drilled with two orifices on both side surfaces. They observed the optimal orifice size was in the range of 0.25–1.41 mm. It has also been observed that hydrophilic plasticizer polyethylene glycol (PEG) with MW of 300 000 g/mol improved drug release, whereas hydrophobic plasticizer triacetin depressed drug release when they were incorporated in CA membrane. The monolithic osmotic tablet system was found to be able to deliver nifedipine at the rate of approximate zero-order up to 24 h [20].

Hai Bang Lee 2000: Had prepared sandwiched osmotic tablet core surrounded by a cellulose acetate membrane with two orifices on both side surfaces delivering nifedipine. The size of orifice observed was in the range of 0.50–1.41 mm. It was also found that the drug release rate of SOTS could be increased by incorporating hydrophilic plasticizer in the membrane, whereas it decreased with hydrophobic plasticizer. Release profile shows a constant rate up to 24 h and independence of release media and agitation rate [21].

Pradeep R. Vavia 2002: Studied about controlled porosity osmotic pump-based drug delivery system where the membrane is accomplished by the use of different channeling agents in the coating. The model drug was pseudoephedrine with an aim to develop a controlled release system for a period of 12 h. Pseudoephedrine of 60 mg has to be taken three or four times daily. Plasma half life is short *i.e.* of 5–8 h. Cellulose acetate (CA) was used as the semi permeable membrane. Diethyl phthalate (DEP), dibutylphthalate (DBP), dibutylsebacate (DBS) and polyethylene glycol 400 (PEG 400) were the different channeling agents. Drug release rate increased with the amount of osmogent due to the increased water uptake was found and hence increased driving force for drug release [22].

Zhi-Qiang Jiang 2003: Has studied about a monolithic osmotic tablet system (MOTS) with two orifices on both side surfaces. Water-insoluble

naproxen was chosen as the model drug. Gum arabic was used as an osmotic, suspending, and expanding agent and cellulose acetate (CA) was used as a semi-permeable membrane. Polyethylene glycol 400 (PEG-400) was employed as plasticizer for controlling membrane porosity. The optimal MOTS was found to be able to deliver naproxen at a rate of approximately zero-order up to 12 h in pH 6.8, cumulative release at 12 h is 81%, independent on environment media and stirring rate [23].

Sanjay Garg 2004: Developed and evaluated extended release formulation of glipizide based on osmotic technology. Glipizide release was inversely proportional to the membrane weight but directly related to the initial level of pore former (PVP) in the membrane. Drug release from the developed formulations was independent of pH and agitational intensity, but dependent on the osmotic pressure of the release media. Results of SEM studies showed the formation of pores in the membrane from where the drug release occurred. The numbers of pores were directly proportional to the initial level of pore former in the membrane [24].

Suresh P. Vyas 2004: Had developed a modified two-layered, push-pull osmotic system that can deliver theophylline and salbutamol sulphate simultaneously for an extended period of time. In vitro release studies showed satisfactory controlled release profiles of both drugs. They studied the effect of concentration of pore-forming agent and orifice diameter on the release of both drugs [25].

A. G. Thombrea 2004: Applied osmotic pressure and polymer swelling method to deliver drugs using swellable-core technology (SCT).The SCT formulations consisted of a core tablet containing the drug and a water-swellable component, and one or more delivery ports. Two model drugs, tenidap, and sildenafil were selected for this purpose. Tablet-recovery and pharmacokinetic studies conducted in beagle dogs showed that the *in-vivo* release of drug from SCT formulations was comparable to the in vitro drug release [26].

Longxiao Liu 2006: Had prepared a monolithic osmotic pump tablet by coating the indented core tablet compressed by the punch with a needle. Atenolol was used as the model drug, sodium chloride as an osmotic agent, and polyethylene oxide as a suspending agent. Ethylcellulose was employed as semi-permeable membrane containing polyethylene glycol 400 as a plasticizer for controlling membrane permeability. The formulation of the atenolol osmotic pump tablet was optimized by orthogonal design and evaluated by the similarity factor (f^2). It was found that from an osmotic tablet, atenolol was delivered at a constant rate up to 24 h, independent of both release media and agitation rate [27].

Longxiao Liu 2008: Had prepared monolithic osmotic pump tablet was obtained by modulating atenolol solubility with acid. Tartaric acid was used as solubility promoter, sodium chloride as an osmotic agent, and polyvinyl pyrrolidone as a retardant agent. Ethylcellulose was employed as a semi-permeable membrane containing polyethylene glycol 400 as a plasticizer. The formulation of an atenolol monolithic osmotic pump tablet was optimized by orthogonal design and evaluated by the similarity factor (f^2). It was found that the monolithic osmotic pump tablet delivered atenolol at a zero-order rate up to 24 h [28].

H. Kranz 2008: Developed a controlled release (CR) multiple unit pellet formulation for SAG/ZK with pH-independent drug release. Pellets with a drug load of 60% were prepared by extrusion/spheronization followed by CR-film coating with an extended-release polyvinyl acetate/polyvinyl pyrrolidone dispersion (Kollidon SR 30 D). Osmotically active ingredients (sodium and potassium chloride, and sucrose) were added to increase the imbibition of aqueous fluids into the pellet cores. According to the outcomes, pH-independent osmotically driven SAG/ZK release was achieved from pellets containing osmotically active ingredients and coated with an extended and enteric polymer [29].

Longxiao Liu 2008: Described a bilayer-core osmotic pump tablet (OPT) which does not require laser drilling to form the drug delivery orifice. The model drug was Nifedipine. Sodium chloride was used as an osmotic agent, Poly-vinylpyrrolidone as a suspending agent, and Croscarmellose sodium as an expanding agent. By ethyl cellulose as a semi-permeable membrane containing polyethylene glycol 400, the indented core tablet was coated for controlling the membrane permeability.

The formulation of the core tablet was optimized by orthogonal design, and the release profiles of various formulations were evaluated by the similarity factor (f^2). The optimal OPT was able to deliver nifedipine at an approximate zero-order up to 24 h, independent on both release media and agitation rates [30].

Wei Li, Gani Du 2008: Had developed a novel push-pull osmotic pump (PPOP) for delivery of water-insoluble drug gliclazide. Compared to conventional PPOP, which only had orifice(s) on the side of the drug layer, the novel PPOP had orifices of the same diameter on both side surfaces. They have found that the drug-release rate of both kinds of PPOP could be influenced by coating level and core hardness, whereas orifice size did not have much influence on it. Poiseuille's law of lamina flow has been used for the illustration of the drug release profile. *The in-vivo* study also showed a good *in-vitro in-vivo* correlation [31].

JavadShokriet 2008: Designed elementary osmotic pump (EOP) tablet for efficient delivery of poorly water-soluble/practically insoluble drugs i.e., indomethacin. Drug release from the system, called swellable elementary osmotic pump (SEOP), is through a delivery orifice in the form a very fine dispersion ready for dissolution and absorption. The optimum aperture diameter for the formulations studied was determined to be 650 lm for zero-order release pattern [32.]

Karsten Mäder 2009: Investigated the drug release from push–pull osmotic systems (PPOS) by Magnetic Resonance Imaging (MRI) using a new benchtop apparatus. The results showed that (i) hydration and swelling critically depend on the tablet core composition, (ii) high osmotic pressure developed by the push layer might lead to bypassing the drug layer and incomplete drug release, and (iii) the hydration of both the drug and the push layers needs to be properly balanced to efficiently deliver the drug [33].

Kenneth C. Waterman 2009: Developed a new controlled-release, extrudable core system (ECS) tablet which osmotically delivers high doses of low solubility active pharmaceutical ingredients (API's). The core contains hydroxyethylcellulose, which serves to entrain the API particles as they are extruded out a hole in the coating at one end of the tablet and sugar, which provides the osmotic driving force for water imbibing. The dosage form has been successfully shown to control the delivery of API over a range of delivery rates, even with 50% of the tablet being API (up to about 500 mg) [34].

Vincent Malaterre 2009: Aimed to understand the factors which had an effect on the drug delivery for modelling the drug release and to develop a mathematical model predictive of the drug release kinetics. Two model drugs were taken to test the influence of the drug property *i.e.,* isradipine (ISR) and chlorpheniramine (CPA), which are practically insoluble and freely soluble, respectively. They have predicted that the influence of each key formulation factors on the release mechanism telling their applicability range and more efficient push pull osmotic pump was designed [35].

R. Kumaravelrajan 2010: Developedthe sandwiched osmotic tablet system that could deliver Nifedipine and Metoprololtartarate simultaneously for an extended period of time. Polyethylene oxide 600,000 and 8,000,000 g/mole were used as a thickening agent of the drug layer and the expandable hydrogel of the push layer, respectively. It was found that the osmotic pump tablet delivers both drugs at a rate of approximately zero-order for up to 16 h independent of pH and agitational intensity, but dependent on the osmotic pressure of the release media [3]6.

Wichan Ketjinda 2011: Had prepared push–pull osmotic tablets (PPOT) of felodipine using an interpolymer complex of chitosan (CS) and poly (acrylic acid) (PAA) as an osmopolymer, and studied the mechanisms ofco its drug release. In the preparation of PPOT, the fabrication of bilayered tablets with the drug layer, containing felodipine, polyethylene oxide, and the polymeric expansion layer, containing the CS–PAA complex was involved.

Drug release from PPOT exhibited zero-order kinetics and could be prolonged up to 12 or 24 h depending on the plasticizer involved. PPOT using dibutylsebacate showed a longer lag time and slower drug release than that using polyethylene glycol 400 [37].

Wen-Jin Xu 2011: Had prepared controlled porosity osmotic pump tablets (CPOPT) for salvianolic acid (SA) and optimized with experimental design methods, including an artificial neutral network (ANN) method. Based on the effects on the drug release rate, three causal factors, i.e., drug, osmotic pressure promoting agent rate, PEG400 content in coating solution and coating weight, were evaluated. The weight expression Y¼ (1_Y1) 2þY2 2 was used in the calculation. Accordng to the results, it was found that the release rate of salvianolic acid B and that of the total salvianolic acid was consistent in the optimized formulation [38].

Xiongkai Cheng 2011: Had designed and evaluated an osmotic pump-based drug delivery system for controlling the release of Ambroxol Hydrochloride. Osmotic agents used were citric acid, lactose, and polyethylene glycol 6000 (PEG 6000). Surelease EC containing polyethylene glycol 400 (PEG 400) controlling the membrane porosity was used as a semi-permeable membrane. The orthogonal design was used for the optimization of the formulation of tablet core and evaluated by the weighted mark method. The release of Ambroxol Hydrochloride from an osmotic pump tablet was verified at a rate of approximately zero-order, and the cumulative release percentage at 12 h was 92.6%. The relative bioavailability of Ambroxol Hydrochloride osmotic pump tablet in rabbits relative to the sustained commercial capsule was 109.6% [39].

Zhi-hong Zhang 2011: Designed push-pull osmotic pump tablets (PPOP) containing different poorly water-soluble drugs and pharmaceutical excipients, and the designed model was established based on the prediction model of release behavior, which was the nucleus of the inference engine. They have used the backpropagation (BP) neural network, which is good at nonlinear mapping and learning function. Finally, the expert system program was constructed by VB. NET associating with SQL Server. Famotidine, a water-insoluble drug, was chosen as the model drug to validate the applicability of the developed expert system [40].

Adarsh Shah 2012: Hadprepared an oral push-pull system that can deliver Ropinirole hydrochloride for an extended period of time. A bilayer osmotic drug delivery system was developed using the drilling technique. The drug release profile showed zero-order kinetics. They developed a push-pull osmotic system which was having desired once-a-day release kinetic [41].

Weisan Pan 2013: Focused for developing an ascending release push-pull osmotic pump (APOP) system using paliperidone to obtain the non-zero order drug release by breaking the balance between the drug suspension release rate in the drug layer and the swelling rate of the core, and an ascending drug release rate was achieved when the former was slower than the latter. To slow down the hydration rate of drug layer, a polymer (Polyox WSR N-12K) was introduced as a suspension agent in drug layer. *In-vitro*, Paliperidone was delivered successfully by APOP at an ascending release rate up to 20 h. The *in-vivo* plasma concentration of paliperidone in beagle dogs increased gradually up to 19 h [42].

Rohit Sharma 2014: Studied on formulation and evaluation of osmotically controlled drug delivery system of carbamazepine, and they also attempted two different approaches, *i.e.*, first one with an osmotic agent and another one an extended-release agent to control the release of the drug. Cellulose acetate and a pore former (plasticizer) were used as the coating solution to coat the core tablets to give good film properties. Formulations prepared gave release more than 70% of the drug after 24 h, and zero-order kinetics was found by the drug released from optimized formulation [43].

Thomas P. Farrell 2014: Had prepared Push-pull osmotic pump (PPOP) tablets of a practically insoluble model drug and the effect of various formulation and process parameters on tablet performance was evaluated. Investigations were done on the influence of varying doses and aqueous solubility of other model drugs (i.e., theophylline, acetaminophen, and verapamil HCl) on the developed PPOP template [44].

Hadjira Rabti 2014: Designed a new EOP tablet of carbamazepine containing a solubility enhancers and swellable polymer, so that side effects will get reduced and improve patient compliance. The effect of different variables of core and coat formulations on drug release behavior was

optimized by Taguchi orthogonal design with analysis of variance (ANOVA) was investigated. According to the outcomes, CBZ solubility was successfully enhanced by a minimum amount of combined polyvinyl pyrrolidone (PVP K30) and sodium lauryl sulfate (SLS). The successful formulation of CBZ-EOP tablets delivered about 80% of CBZ at a rate of approximately zero-order for up to 12 h was delivered [45].

Tejal A. Mehta 2014: Studied to develop elementary osmotic pump tablets containing Flurbiprofen using an inclusion complex. They revealed the osmotic agent and size of the delivery orifice, which had a significant effect on % release to achieve a zero-order drug profile [46].

Pooja V. Kadu 2016: Hd improved the site specification and provided the controlled release of drugs for a once-a-day drug delivery system. With the help of 32 Factorial Designs, Bilayer Push-Pull Osmotic Pump tablet of Atenolol was formulated, optimized, and evaluated. It was found that the drug release is affected by the use of suspension agents in drug layer. According to the results, the effect of orifice diameter, polymer concentration in the drug layer, coating composition, and plasticizer amount gave promising outcomes. The peppas model has been followed for the release kinetics [47].

Ali Nokhodchi 2017: Investigated controlled porosity osmotic pump (CPOP) system using nano-suspension coating method. 4-Amino pyridine was chosen as the model drug. The formulations was assessed in terms of D12 h (cumulative release percent after 12 h), Devzero(mean percent deviation of drug release from zero-order kinetic), Tl (lag time of the drug release) and RSQ zero. The results revealed that gelling agent amount (HPMC E15LV) in core and pore former concentration in SPM had a crucial effect on SPM integrity [48].

Jesse Zhu 2017: Had prepared dry powder coated osmotic drug delivery system (ODDS) and characterized using an innovative powder coating technology. Firstly by electrostatic spray gun coating powder adhered to the surface of the ODDS core, followed by a curing step to allow those electrically deposited particles coalesce and form a continuous, uniform, and strong coating film, which is the semi-permeable membrane of the ODDS. Both in reducing the glass transition temperature of the coating polymer (cellulose acetate) and in increasing the electrical conductivity of the ODDS cores, triethyl citrate (TEC) was found to be a better liquid plasticizer than PEG 400, which led to an enhanced coating powder adhesion and film formation. The model drugs were Salbutamol sulfate and ibuprofen. Zero-order drug release kinetics was achieved [49].

Takehisa Nakajima 2018: Prepared an elementary osmotic pump (EOP) using polyethylene oxide (PEO) and NaCl as an excipient, and the influence of the molecular weight of PEO on drug-release was investigated. The dissolution profile of EOP was Sigmoidal, and in spite of the short time, a zero-order release region was observed. Next, a push-pull pump (PPP) with an almost identical formulation to that of EOP was prepared, and according to the outcomes, PPP using a low-molecular-weight PEO for the drug layer and PEO with a high-molecular-weight in the push layer showed the longest dissolution profile of the linear region [50].

Gensheng Yang 2018: Had used an electrostatic coating technology with ultrafine powders to form a novel controlled porosity osmotic pump. Ultrafine coating powders were electrostatically deposited onto the surface of osmotic pump cores with an electrostatic spray gun, followed by a curing step to allow those deposited ultrafine particles to coalesce and form a continuous coating film contains the film-forming polymer (cellulose acetate, CA) and pore former. In increasing the flowability of the ultrafine coating powders, colloidal silicon dioxide was found to be efficient, leading to a higher coating powder adhesion rate and more uniform coating film. It was found that the dissolution tests and the modeling of the drug release profiles followed zero-order drug release kinetics [51].

Weisan Pan 2018: Developed actarit double-layered osmotic pump tablets to overcome the weak points of actarit common tablets, such as short half-life and large plasma concentration fluctuations. To optimize the formulation, Single-factor experiment and orthogonal test were applied. The pharmacokinetic study was performed in beagle dogs adopting actarit common tablets as reference tablets. Formulation followed was: drug

layer: 150 mg actarit, 240 mg PEO-N80, 50 mg NaCl; push layer: 140 mg PEO-WSR303, 20 mg NaCl; coating solution: 30 g cellulose acetate and 6 g PEG 4000 in 1000 ml 94% acetone solution, 60 mg coating weight gain. According to the pharmacokinetic study, T max was prolonged by the contrast of common commercial tablets with a constant drug release rate, but the bioavailability was equivalent. The actarit osmotic pump tablets established a good *in-vivo* in vitro correlation [52].

B. S. Venkateswarlu 2019: Reviewed that osmotic pressure can be used for the delivery of drugs by the process of osmosis in osmotic drug delivery with the help of different osmogens. This kind of delivery has many applications in the field of pharmaceuticals of humans as well as veterinary. When a dosage form of osmotic delivery goes into the external environment creates osmotic pressure and releases the drug from the device. The osmotic device consists of an inner core containing drug and coated with a semi-permeable membrane in the oral delivery systems and implantation. Osmotic pumps, and it is the most promising controlled drug delivery system [53].

Evaluation of Osmotic Drug Delivery System: Oral osmotic drug delivery system can be evaluated using the following parameters. Visual appearance: visual inspection of the film can be done for smoothness, uniformity of coating, edge coverage, and luster [54, 55, 56, 57]. Coating uniformity: the uniformity of coating among the tablets can be estimated by determining the weight, thickness, and diameter of the tablet before and after the coating. Coat weight and thickness: it can be determined from depleted devices following careful washing and drying of the film, using a standard analytical balance and screw gauge, respectively. Orifice diameter: the mean orifice diameter of an osmotic pump tablet can be determined microscopically using a pre-calibrated ocular micrometer.

***In-vitro* Evaluation:** The conventional USP and basket type apparatus have been used for the in-vitro release of drugs from the oral osmotic system.USP described the use of commercial standard dissolution apparatus and commercial applied analytic standard dissolutions apparatus. The dissolution medium is generally distilled water as well as simulated gastric fluid (for 2-4 h), and intestinal fluids have been used.

The standard specifications which are followed for oral controlled drug delivery system are equivalently applicable for oral osmotic pumps.

***In-vivo* Evaluation:** The *in-vivo* evaluation of the oral osmotic system has been carried out mostly in dogs and monkeys. As the environment in the intestinal tract of the dogs is quite similar to that of the human beings in terms of pH and motility, dogs have been widely used for *in-vivo* delivery rate measurement of drugs from oral osmotic drug delivery systems and to established in-vitro in-vivo correlation.

Marketed Products: [58, 59, 60, 61]

Product Name	Active Pharmaceuticalingredient	Design of Osmotic Pump
Acutrim	Phenylpropanolamine	Elementary pump osmotic pump
Alpresslp	Prazosin	Push-pull osmotic pump
Cardura xl	Doxazosin	Push-pull osmotic pump
Chronogesic tm	Sufentanil	Implantable osmotic system
Coverahs	Verapamil	Push-pull osmotic pump
Ditropan xl	Oxybutinin chloride	Push-pull osmotic pump
Dynacirccr	Isradipine	Push-pull osmotic pump
Efidac 24	Pseudoephiderine	Elementary pump osmotic pump
Efidac 24	Chlorpheniraminemeleate	Elementary pump osmotic pump
Glucotrol xl	Glipizide	Push-pull osmotic pump
Invega	Paliperidone	Push-pull osmotic pump
Minipress xl	Prazocine	Elementary pump osmotic pump
Procardia xl	Nifedipine	Push-pull osmotic pump
Sudafed 24	Pseudoephiderine	Elementary pump osmotic pump
Viadur	Leuprolide acetate	Implantable osmotic system
Volmex	Albuterol	Elementary pump osmotic pump

CONCLUSION: Osmotic drug delivery system has come a long way since the discovery of the first osmotic device. In the Osmotic Drug Delivery system, osmotic pressure provides the driving force

for drug release. Present-day osmotic delivery system devices not only seek to deliver a variety of agents (i.e., high, moderate, or low solubility and liquid formulations) but are also capable of modulating drug release OROS products are designed to meet the desired delivery profile for the specific drug and its therapeutic indication. The major advantages include accurate control of zero-order or another patterned release over an extended time period, consistent release rates can be achieved irrespective of the environmental factors at the delivery site. This study highlighted the robustness, and yet flexibility, of the osmotic system for various model drugs.

- There are no conflicts of context.

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CONFLICTS OF INTEREST: Nil

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