

Unlocking the Potential of Osmotically Controlled Drug Delivery System: A Comprehensive Review

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ABSTRACT

One of the greatest medication delivery systems available today is osmotically controlled, as it is exceedingly successful and efficient. Osmotic drug delivery devices use the energy-distribution principle of osmotic pressure to deliver medications. Numerous biomedical benefits can be derived from oral osmotic drug delivery systems due to their adaptability and extremely consistent drug release rates. Since osmosis is the transfer from a lower concentration to a higher concentration, osmotic pressure is used in this situation to administer the medication appropriately. This approach allows us to release drugs in an appropriate manner because it is a widely recognized technique with intriguing applications and facts. Like pharmaceuticals, there are different drug delivery components. Each semi-permeable membrane and osmotic agent has a specific function and is necessary. It is one of the best in best method used now a days to get best results.

Keywords: Osmosis, drug delivery, controlled, semipermeable, drug

INTRODUCTION

Oral Drug Delivery System:

Comparing oral medication delivery to all other known drug delivery routes, it is the most widely recognized and utilized method of administration.¹ The drug is released instantly from conventional oral drug delivery methods, making it impossible to regulate the drug's release and sustain an effective concentration at the site of action or target for an extended period of time.² These pave the path for the creation of further medication delivery systems with modified release. ^{3,4}

Mathematical Models for Controlled-Release Kinetics⁵:

From the perspective of mathematical modeling, controlled-release systems can be categorized based on the physical mechanisms governing the release of integrated solute. Most controlled-release systems rely on diffusion, dissolution, or a mix of the two to produce a drug's gradual release. Based on this, a range of controlled release delivery methods are available, including:

1. Dissolution – controlled release
2. Osmotically – controlled release
3. Diffusion – controlled release
4. Chemically – controlled release
5. Miscellaneous – controlled release

Osmotic Controlled Delivery System:

The osmosis concept underlies the operation of an osmotic controlled delivery system. Controlling the pace at which the active ingredient is delivered, extending the duration of therapeutic activity, and/or directing administration to a particular tissue are the primary goals of modified release. These developments led to the creation of osmotic pumps, a type of drug delivery system with membrane control that draws energy from osmotic pressure. The basic idea is that water percolates across a semi-permeable membrane, which permits water to pass through without the active component dissolving its contents and pushing them off.⁶

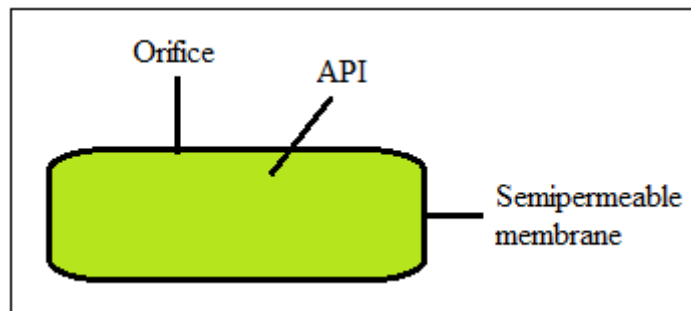


Figure-1: Schematic cross section of a one chamber osmotic pump⁷

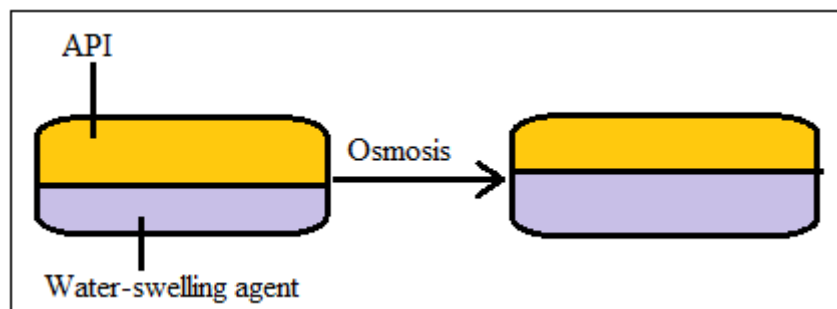


Figure-2: Mechanism of action of a two-chamber osmotic pump tablet⁷

The type, surface area, and thickness of the semi-permeable coating can be altered during formulation to determine the desired release rate of the API.

The type of media that facilitates the API.

How big the orifice is.

The nature of the water-swelling osmotic agent.

Osmotic pump administration has an advantage over modified release dose forms since it releases the API steadily and tends to have zero order kinetics, or a release rate that is independent of the medication. This idea can be used to the therapy of diabetes, arthritis, and hypertension.⁶ In the US, EU, Japan, etc., there are more than 357 patented osmotic drug delivery systems.⁸

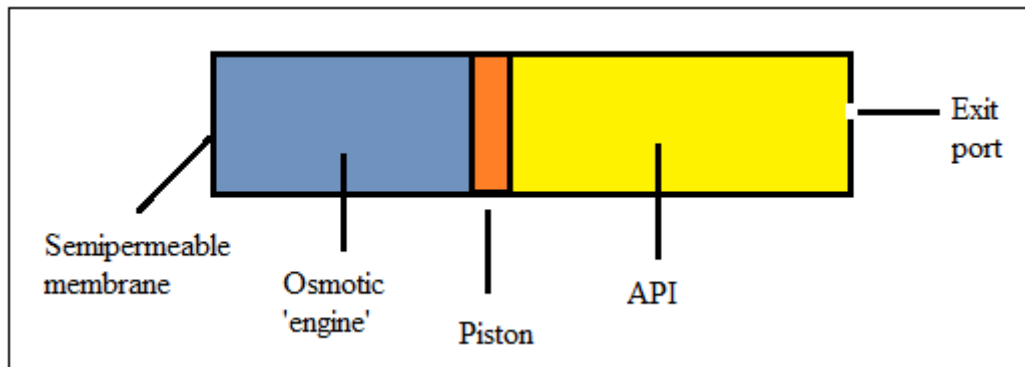


Figure-3: Schematic cross-section of a typical osmotic pump implant⁷

Osmosis:

The net flow of water across a semi-permeable membrane from a region with a high concentration of water to one with a low concentration is known as osmosis. A semi-permeable membrane is one that permits the passage of water through it but not other substances⁹.

Classification of Osmotic Drug Delivery System¹⁴:

A general classification consisting of oral and implantable systems can be considered as follows.

- **Implantable**
- **Oral**
- **Specific types**

Implantable Osmotic Pumps:

- Rose-Nelson Pump
- Higuchi Leeper Pump
- Higuchi Theuwes pump

Oral Osmotic Pumps:

The oral osmotic systems can be of various types which are as follows

- Single chamber osmotic pump - Elementary Osmotic Pump
- Multi chamber osmotic pump - Push pull osmotic pump

Specific types:

- Controlled porosity osmotic pump
- Osmotic bursting osmotic pump
- Liquid Oral Osmotic System(L-OROS)
- Delayed delivery osmotic device
- Telescopic capsule
- OROS – CT (Colon Targeting)
- Sandwiched oral therapeutic system
- Monolithic osmotic systems
- Multi -Particulate Osmotic Pump

Implantable Osmotic Pumps:

Rose-Nelson Pump¹⁵:

Rose and Nelson, are the two scientists were the initiators of osmotic drug delivery. In 1955, they developed an implantable pump for the drug delivery to the cattle and sheep gut. The Rose-Nelson implantable pump is composed of 3 chambers

1. a drug chamber
2. salt chamber holding solid salt,
3. water chamber.

A semi-permeable membrane separates the salt from water chamber. The water movement from the water cavity towards salt cavity is influenced by difference in osmotic pressure across the membrane. Possibly, the volume of salt cavity increases due to water flow, which swells the latex diaphragm dividing the salt and drug chambers: finally, the drug is pumped out of the device.

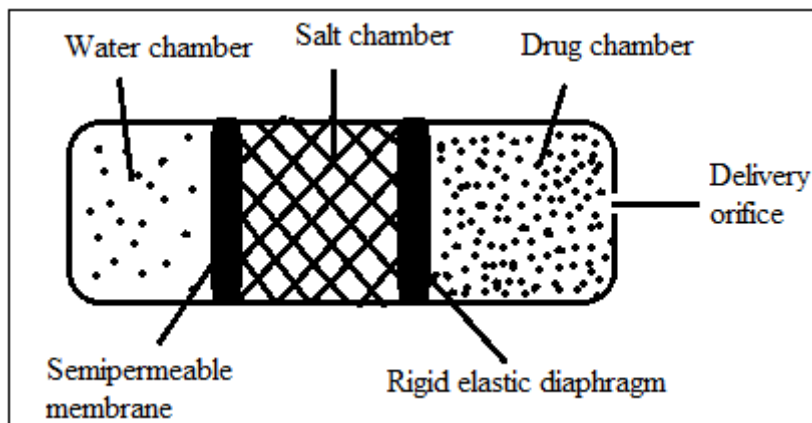


Figure-4: Rose-Nelson Pump¹⁵

Higuchi-Leeper Osmotic Pump¹⁵:

Numerous Rose-Nelson pump modifications have been proposed by Higuchi and Leeper, and they have been detailed in US patents that represent the Alza Corporation's simplifications of the Rose-Nelson pump. The Higuchi-Leeper pump lacks a water cavity, and water from the surrounding environment is ingested before the device is activated. This distinction makes it possible to preload the device with a drug load and store it for a long time before using it. This kind of pump often has a salt cavity with a fluid solution with an excess of solid salt; it also has a hard housing and a semi-permeable membrane mounted on a perforated frame. Following injection, the magnesium sulfate is broken down by surrounding biological fluid entering the device through a semi-permeable, porous membrane. This creates osmotic pressure inside the device, pushing a movable separator toward the drug cavity to remove the drug from the device. Veterinarians utilize it extensively. This kind of pump is implanted within an animal's body to provide growth hormones or antibiotics.

Higuchi-Theeuwes Pump¹⁵:

Higuchi and Theeuwes in early 1970s developed another variant of the Rose-Nelson pump, even simpler than the Higuchi-Leeper pump as illustrated in Figure.

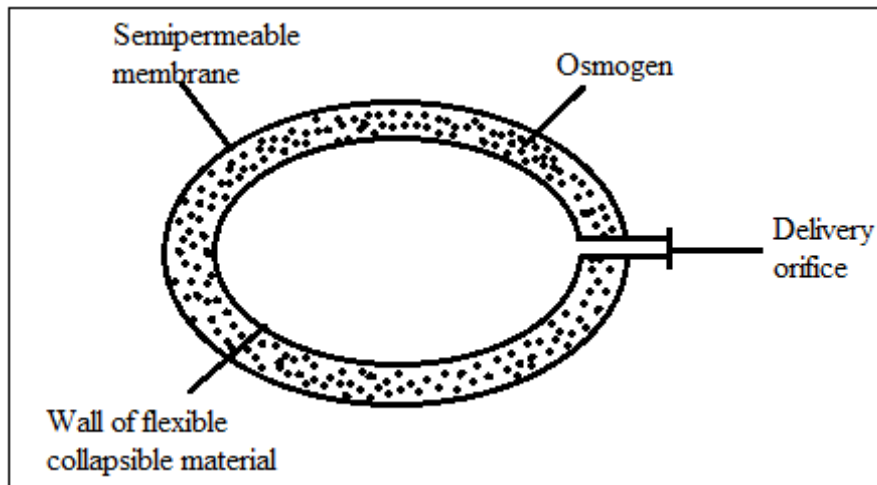


Figure-5: Higuchi-Theeuwes pump¹⁵

This gadget has a semi-permeable membrane as its rigid casing. This membrane is robust enough to resist the pumping pressure that water imbibitions create inside the device. The medicine is only loaded prior to application, increasing the device's advantage for long-term storage. The salt utilized in the salt cavity and the outer membrane's permeability properties control the drug release from the apparatus.

Oral Osmotic Pumps:

Elementary Osmotic Pump¹⁵:

The fundamental osmotic pump, a more straightforward version of the Rose-Nelson pump, made osmotic administration a key strategy for obtaining controlled medication release. Figure depicts Theeuwes' 1974 invention, an elementary osmotic pump with an active component with an appropriate osmotic pressure. It is created as a tablet, often using cellulose acetate, covered in a semi-permeable membrane. A tiny hole is bored into the membrane layer. As soon as the coated tablet comes into contact with liquid, water is drawn through the semi-permeable coating by the drug's osmotic pressure, creating a saturated aqueous solution inside the apparatus. Since the membrane is non-extensible, the water imbibitions cause the tablet's volume to grow, which in turn increases the hydrostatic pressure inside the tablet and allows solution that is saturated with the active agent to flow out of the device through a tiny hole.

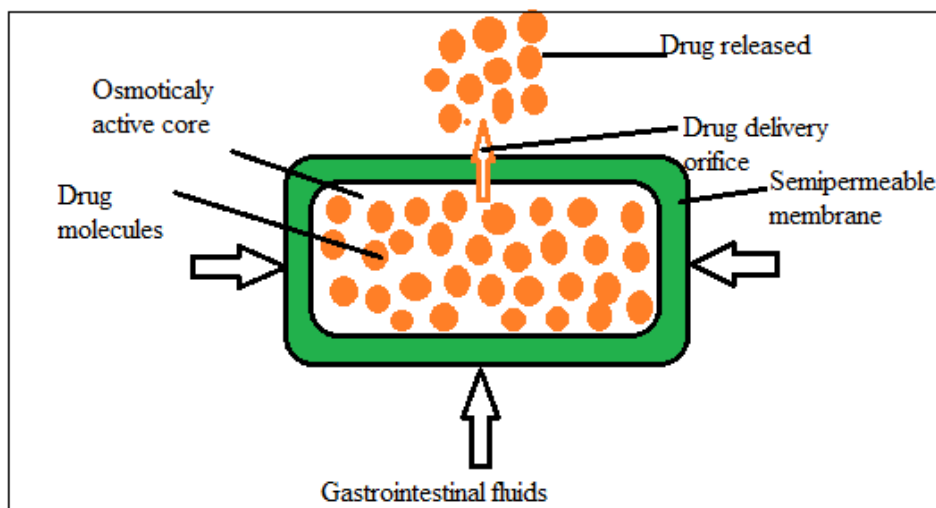


Figure-6: Elementary osmotic pump¹⁷

Push-Pull Osmotic Pump (PPOP) ¹⁵:

An adjustment to EOP is the push-pull osmotic pump. Drugs that are highly and poorly water soluble are delivered at a consistent rate via a push-pull osmotic pump. This device has the appearance of a typical bi-layer coated tablet.

Specific Types:

Controlled Porosity Osmotic Pump (CPOP) ¹⁵:

Figure shows the controlled porosity osmotic pump (CPOP). This is an osmotic tablet in which the water-soluble pore-forming chemicals (such as urea, nicotinamide, sorbitol, etc.) that are part of the semi-permeable membrane (SPM) escape to form the delivery holes in-situ. The degree of drug solubility in the tablet core, the thickness of the coating, the amount of leachable pore-forming agent(s), and the osmotic pressure difference across the membrane all affect how quickly drugs release from a controlled porosity osmotic pump. The CPOP system is really beneficial. Since the medication is released from the entire device surface rather than just one hole, the issues with stomach irritation are significantly reduced. Furthermore, since the holes are created in-situ, a complex laser-drilling unit method is not necessary. The drug release phenomena is described by Scheme from a typical CPOP.

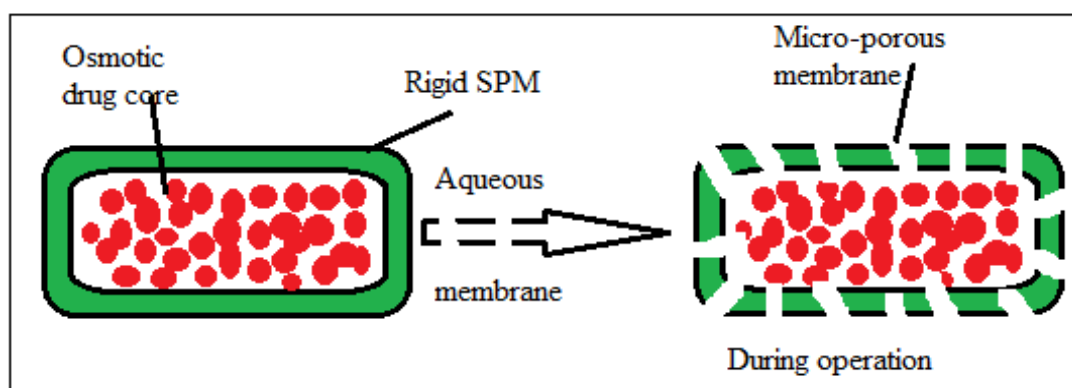


Figure-7 : Controlled porosity osmotic pump¹⁹

Bursting Osmotic Pump¹⁹:

Osmotic bursting osmotic pumps and elementary osmotic pumps are closely related to each other. The lack of a delivery valve and the tiny size of the osmotic pump are the two main distinctions between the two types of osmotic pumps.

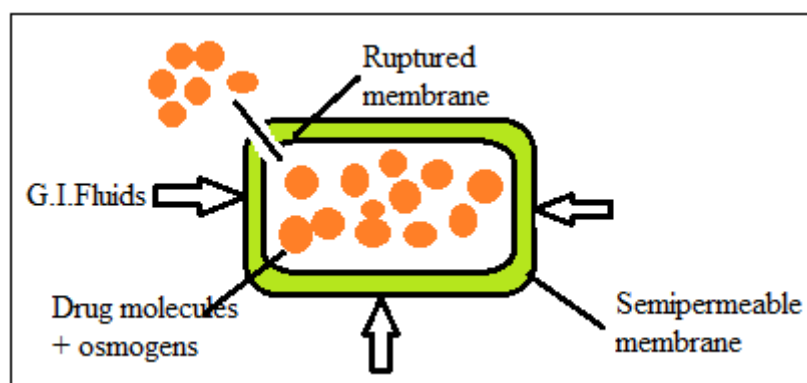


Figure-8: Bursting osmotic pump¹⁹

Liquid OROS¹¹:

Liquid oral osmotic system are designed to deliver the drugs as liquid formulations and combine the benefits of extended release with high bioavailability. They are of three types:

- L-OROS hard cap,
- L-OROS soft cap,
- Delayed liquid bolus delivery system

A semi-permeable membrane covering, an osmotic engine or push layer, and a liquid medication layer are components of each system. Depending on the permeability of the rate-controlling membrane and the thickness of the placebo layer, drug release may be postponed for one to ten hours.¹⁹

Delayed Delivery Based on Multiple Coating²⁰:

Fluid is delivered by this osmotic device after a predetermined and adjustable time period. One can customize the size of the osmotically powered pump to make it suitable for implanting or swallowing. After a brief activation period, during which almost no medication is given, this is used to administer a medicine in a fluid form.

Telescopic Capsule^{20, 21}:

It is a device that delivers an active agent both instantly and over an extended length of time. The dispenser has a telescoping sliding configuration made up of first and second wall parts. The device is made up of two chambers: an osmotic engine and an exit port are located in the second chamber, which also holds the medicine.

Colon Targeted Oral Osmotic System (OROS-CT)¹⁴:

It could have one osmotic device or five or six osmotic devices packed into a hard gelatin capsule. The osmotic system has an enteric covering.

Osmotic Sandwiched Tablet/Pump (SOT)¹⁴:

Core and coat make up the SOT. The coat is made out of a semi-permeable membrane with a delivery hole on both sides. Three layers make up the core tablet: a central push layer containing the medication and two connected layers.

Osmotic Systems in Monoliths¹¹:

This monolithic osmotic system is made up of chemicals that dissolve in water dispersed across a polymer matrix. When this system enters the watery zone, the active agent imbibitions water. This occurs when the polymer matrix capsule enclosing the medicine ruptures, releasing it. This reaction initially occurs in the polymeric matrix's outermost region before moving inside the matrix. This method fails if 20–30 volumes per liter of the active agents are used. There is a notable contribution from the substance's simple leaching.

Multi-Particulate Osmotic Pump²⁰:

This kind of osmotic pump is characterized by a tablet or capsule containing a high number of pellets that contain two or more pellets or particle populations. Each pellet has a core made up of a water-

soluble osmotic agent and the therapeutic medication. A water-permeable yet water-insoluble polymer layer surrounds each core.

Formulation of Osmotic Controlled Drug Delivery System:

Following are the basic components of osmotic drug delivery system:

Drug¹⁴:

Medicines with a shorter terminal half-life (between one and six hours) and greater potency for longer treatment periods are more suited for osmotic controlled releases. Numerous potential medications, include paliperidone and glipizide, The formulation of nifedipine is for osmotic distribution.

Osmotic Agent^{14, 22}:

The concentration gradient across the membrane is maintained by osmogents, also known as osmotic agents. Pushing force is created during the absorption of water and aids in the hydrated formulation by preserving the homogeneity of the medication. The osmotic components are ionic substances made up of hydrophilic polymers or inorganic salts. Osmotic agents include lithium or potassium chloride, sodium chloride, and potassium or sodium sulfates.

Table-1: Osmotic agents and their examples

Osmogens	Example
Inorganic water-soluble osmogens	Sodium bicarbonate, Sodium sulphate, Magnesium sulphate, Sodium chloride, Potassium chloride
Organic polymer osmogens	Hydroxy propyl methyl cellulose, Sodium carboxy methyl cellulose, Polyethylene oxide, Polyvinyl pyrrolidone, methyl cellulose
Carbohydrates	Arabinose, mannose, galactose, ribose, glucose, fructose, sucrose, maltose, lactose, xylose
Water-soluble amino acids	Alanine, glycine, leucine, methionine

Pore Forming Agents^{14, 23}:

Pore-forming chemicals are employed in the development of multiparticulate osmotic pumps and controlled porosity pumps, which are designed for drugs that are poorly soluble in water. These agents generate microporous membranes. Leaching that takes place throughout the procedure causes microporous development to occur in-situ. The pores in the wall are caused by the gas that was produced in the coating polymer solution before the gadget was operated. The pore-formers ought to be non-toxic and ought to cause channels to develop when they are removed. The channels turn into a fluid transmission route.

- ✓ Alkaline earth metals like calcium chloride and calcium nitrate;
- ✓ Alkaline metal salts like potassium chloride, sodium chloride, sodium bromide, and potassium sulphate, among others.
- ✓ Sugars and carbohydrates, including mannose, lactose, glucose, fructose, sorbitol, mannitol, and diols.

Wicking Agent²²:

A wicking agent is a substance that has the capacity to pull water into a porous network. Either swellable or non-swellable characteristics apply. They are able to physisorb (attach themselves to water).

Alumina, niacinamide, m-pyrol, bentonite, magnesium aluminum silicate, polyester, titanium dioxide, sodium lauryl sulphate (SLS), colloidal silicon dioxide, kaolin, low molecular weight poly vinyl pyrrolidone (PVP), and polyethylene.

Flux Regulating Agents^{14, 22}:

These are combined with materials that form well. These chemicals aid in controlling the fluid permeability of the flux through the wall. They can be chosen in advance to increase or decrease the liquid flow. Additionally, they divide the lamina's porosity and flexibility.

- ✓ Hydrophilic compounds, such as polyethylene glycol (300–6000 Da), polyhydric alcohol, and poly alkylene glycol, are agents that enhance flux.
- ✓ Hydrophobic compounds like phthalates that are replaced with an alkyl or alkoxy are known as flux reduction agents; diethyl phthalate and dimethoxy ethyl phthalate are two examples.

Semi-Permeable Membrane^{11, 14, 23}:

The key characteristic of the semi-permeable membrane used in an osmotic pump is that it only allows water to enter the device, effectively isolating the dissolution process from the intestinal environment. Water-permeable polymers, such as cellulose acetate, agar acetate, betaglucon acetate, ethyl cellulose, polyether copolymer, olyacetals, polyglcolic acid, polyactic acid, sulfonated polystyrenes, and polyurethanes, can be employed as coating materials in osmotic devices.

Coating Solvent^{2,23}:

Inert inorganic and organic solvents that do not negatively impact the core wall and other excipients in osmotic drug delivery are excellent for creating polymeric solutions, which are utilized to manufacture the wall of the osmotic device. A mixture of solvents such as acetone-methanol(80:20), methylene chloride-methanol(79:21), acetone-ethanol(80:20), methylene chloride-methanol-water (75:22:3), and methylene chloride, methanol, isopropyl alcohol, dichloromethane, ethyl acetate, acetone, carbon tetrachloride, cyclohexane, butyl alcohol, and water are some examples of coating solvents.

Plasticizers²²:

Plasticizers reduce the temperature at which the wall's elastic modules or second order phase transition occurs. Additionally, it makes the fluids more pliable, flexible, and workable.

Wall-forming ingredients are mixed with plasticizer in quantities ranging from 0.001 to 50 parts, or a combination thereof.

Examples include acetates, propionates, glycolates, glycerolates, myristates, benzoates, sulphonamides, alkyl adipates, trioctyl phosphates and other phosphates, dialkyl phthalates and other phthalates, and triethyl citrate and other citrates.

Factors That Influence The Release Rate In The Osmotic Controlled Drug Delivery Systems: Drug Solubility¹⁹:

One of the key factors influencing the osmotic system's medication release kinetics from osmotic pumps is the drug's solubility. The drug's solubility within the drug core has a direct bearing on the osmotic drug release kinetics. The fraction of released core, assuming a pure drug tablet core with zero-order kinetics, can be found in equation.

$$F(z) = 1 - S/\rho \text{ (Eq. 1)}$$

Where,

F(z) is the fraction released by zero-order kinetics, S is the drug's solubility (g/cm³),

ρ is the density (g/cm³) of the core tablet.

Osmotic Pressure¹⁹:

The osmotic pressure differential that exists between the inside compartment and the surrounding environment is the next release-controlling component that needs to be optimized.

Table-2: Osmotic pressure of different compound and its mixture.

Compound or Mixture	Osmotic Pressure (atm)
Lactose-Fructose	500
Dextrose-Fructose	450
Sucrose- Fructose	430
Mannitol-Fructose	415
Sodium chloride	356
Fructose	335
Lactose-Sucrose	250
Potassium chloride	245
Lactose-Dextrose	225
Mannitol-Dextrose	225
Dextrose-Sucrose	190
Mannitol-Sucrose	170
Sucrose	150
Mannitol-Lactose	130
Dextrose	82
Potassium sulfate	39
Mannitol	38
Sodium phosphate tribase 12H ₂ O	36
Sodium phosphate dibasic 7H ₂ O	31
Sodium phosphate dibasic 12H ₂ O	29
Sodium phosphate dibasic anhydrous	29
Sodium phosphate monobasic H ₂ O	28

Size of Delivery Orifice¹⁵:

The area of the orifice needs to be sufficiently large to minimize the build-up of osmotic pressure in the

system in order to obtain a zero-order delivery profile. If not, the membrane may be deformed by the hydrostatic pressure, which could impact the zero-order delivery rate. As a result, the orifice's cross-sectional area—whose typical size ranges from 600 microns to 1 mm—should be kept optimal between the lowest and highest values.

Semi-Permeable Membrane¹⁹:

When designing an oral osmotic system, a few membrane factors that are crucial to consider are:

- ✓ Polymer type and nature: Any polymer that is impermeable to solutes yet permeable to water may be chosen.
- ✓ Membrane thickness: The drug release from the osmotic system is significantly influenced by the membrane's thickness, and the two are inversely proportional.
- ✓ The kind and quantity of plasticizer:

Plasticizers or low molecular weight diluents are added to pharmaceutical coatings to change the physical characteristics of the polymers and enhance their film-forming abilities.

Evaluation of Oral Osmotic Drug Delivery Systems²⁵⁻³¹ :-

One can assess oral osmotic medication delivery systems for the following reasons:

- **Visual inspection:**
Examine the film visually for shine, edge coverage, smoothness, and consistency of coating.
- **Consistency of coating:**
By comparing the weight, thickness, and diameter of the tablet before and after coating, it is possible to evaluate the degree of uniformity in the coating throughout the tablets.
- **Weight and thickness of coat:**
After the film has been carefully cleaned and dried, the coat weight and thickness can be measured with depleted equipment using a conventional analytical balance and a screw gauge, respectively.
- **Inlet diameter:**
An ocular micrometer that has been previously calibrated can be used to measure the mean orifice diameter of an osmotic pump tablet under a microscope.
- **In vitro release of drugs:**
Many techniques, such as the flow-through apparatus, the traditional USP dissolution apparatus I and II, the vertically reciprocating shaker, etc., can be used to calculate the in vitro delivery rate of pharmaceuticals from osmotic systems.
- **Effect of pH:**
Regardless of outside factors, an osmotically controlled release system distributes its contents. Dissolution media with varying pH levels are employed to verify this.
- **Impact of the degree of agitation:**
Release experiments are conducted in dissolving equipment at different rotational speeds to investigate the effect of agitational intensity of the release media.
- **In Vivo Assessment:**
Human volunteers in good health can also be used for in vivo evaluation. Different pharmacokinetic characteristics

Advances in Osmotic Drug Delivery²⁴:

Duros Technology:

The DUROS pump is conceptually similar to a tiny syringe that is used to inject drugs at precisely controlled, minute amounts. Salt, an osmotic agent found in the engine compartment, progressively draws water from the body through the semi-permeable membrane and into the pump through the process of osmosis. A piston is slowly and continually displaced by the water pulled into the engine compartment, expanding the osmotic agent and causing small amounts of drug formulation to be dispensed via the opening from the drug reservoir.

From ALZA Corporation, DURECT possesses an exclusive license to create and market goods in specific industries utilizing DUROS® implant technology.

Marketed Products¹⁹:

Table -3: Marketed products of osmotic drug delivery system

Trade Name	Active ingredient	Design system	Dose
Alpress LP	Prazosin	Push -Pull	2.5 - 5 mg
Acutrim	Phenylpropanolamine	Elementary pump	75 mg
Cardura XL	Doxazosin	Push -Pull	4, 8 mg
Covera HS	Verapamil	Push -Pull with time delay	180, 240 mg
Ditropan XL	Oxybutinin chloride	Push -Pull	5, 10 mg
Dynacirc CR	Isradipine	Push -Pull	5, 10 mg
Invega	Paliperidone	Push -Pull	3, 6, 9 mg
Efidac 24	Chlorpheniramiemaleate	Elementary Pump	4 mg IR, 12 mg CR
Glucotrol XL	Glipizide	Push - Pull	5, 10 mg
Minipress XL	Prazocine	Elementary pump	2.5, 5 mg
Procardia XL	Nifedipine	Push - Pull	30, 60, 90 mg
Sudafed 24	Pseudoephedrine	Elementary pump	240 mg
Volmax	Sabutamol	Elementary pump	4, 8 mg
Tegretol XR	Carbamazepine	oros	100, 200, 400mg
Viadur	Leuprolide acetate	Implantable osmotic systems	-----
Chronogesic	Sufentanil	Implantable osmotic systems	-----
Concreta	Methylphenidate	Implantable osmotic systems	18, 27, 36, and 54 mg

CONCLUSION:

Since the technique previously mentioned and explained has many applications, it is the most effective way to distribute medications. However, there are certain drawbacks as well, albeit they are manageable with the right attention. This method of delivering pharmaceuticals is widely acknowledged, and the numerous components and pumps employed in it can be quite beneficial if handled with caution and understanding. These approaches are also highly fascinating and productive in the drug industry. Using

osmosis as the primary mechanism for drug administration within a core that has been carefully designed. Osmotic drug delivery systems have become more and more common as a dosage form for controlled drug administration because to its potential benefits, which include drug distribution at zero order rate, release rate not affected by hydrodynamic state or gastric pH, etc. Osmotic drug delivery systems have advanced significantly since its inception 25 years ago, and they are currently utilized as research instruments to examine the distribution of medications with various physicochemical and pharmacokinetic characteristics. The current study set out to develop and assess an osmotic controlled delivery system for an anti-diabetic medication invented by an innovator. The most promising strategy-based systems for regulated drug administration are osmotic devices.

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