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## A REVIEW ON THE OSMOTIC DRUG DELIVERY SYSTEM

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### ABSTRACT

Conventional drug delivery systems often struggle to provide precise control over the release of drugs and targeting them to specific sites within the body, leading to fluctuations in plasma drug concentrations. This unpredictability poses challenges in achieving optimal therapeutic outcomes and can result in undesirable side effects. In response to these limitations, there has been a notable shift towards the development of novel drug delivery systems. Osmotic controlled drug delivery systems are a type of Novel drug delivery systems that utilize osmotic pressure for controlled delivery of active agents. Osmotically controlled drug delivery systems (OCDDS) represent a highly promising technology that harnesses osmotic pressure to precisely regulate the delivery of active agents. Unlike traditional systems, the release of drugs from OCDDS remains unaffected by pH variations and hydrodynamic conditions within the body due to the semi-permeable properties of the rate-controlling membrane and the design of the delivery orifice. This characteristic ensures a strong correlation between in vitro and in vivo performance. Additionally, osmotic drug delivery systems exhibit zero-order kinetics, meaning the release rate remains constant over time and is independent of initial drug concentration and gastrointestinal physiological factors.

**Key words:** Conventional delivery system, Osmotic pressure controlled formulation, Novel drug delivery systems, Osmosis, Osmotic pump.

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### 1. INTRODUCTION

Novel drug delivery systems (NDDS) represent a pivotal area of pharmaceutical research and development due to their comparatively lower costs and shorter development timelines compared to creating entirely new chemical entities. Many traditional drug delivery systems have been devised to regulate the release of a drug over an extended period. There are various designs available to manage or adjust drug release from dosage forms. The majority of controlled-release oral dosage forms fall into matrix, reservoir, or osmotic system categories.

However, conventional matrix or reservoir formulations often encounter issues with fluctuating bioavailability due to changes in gastric pH. Additionally, drug release from these systems can be influenced by the body's hydrodynamic conditions. The rate and degree of drug absorption from conventional formulations may vary significantly depending on factors such as the drug's physicochemical properties, presence of excipients, physiological factors like the presence or absence of food, and the pH of the gastrointestinal tract (GI), among others.

However, drug release from oral controlled-release dosage forms can be influenced by factors such as pH, gastrointestinal (GI) motility, and the presence of food in the GI tract. Osmotically controlled drug delivery systems (OCDDS) represent one of the most promising technologies in drug delivery, utilizing osmotic pressure as a driving force for the controlled release of active agents. The release of drugs from OCDDS is not reliant on pH or the hydrodynamic conditions of the body due to the semi-permeable nature of the rate-controlling membrane and the design of the delivery orifice used in osmotic systems. As a result, OCDDS achieves a high degree of correlation between in vitro and in vivo performance(1-3).

#### Advantages

- They typically give a zero-order release profile after an initial lag.
- The release mechanisms are independent of drug concentration.
- Sustained and consistent blood levels within the therapeutic window.
- Reduced side effects.
- Deliveries may be delayed or pulsed if desired.
- Drug release is independent of gastric pH and hydrodynamic condition.
- They are well-characterized and understood.
- The delivery rate is independent of agitation outside, including GI motility.
- Enhanced bioavailability of drug.
- Reduced inter-patient variability(4).

### Disadvantages

- Expensive.
- If the coating process is not well controlled there is a risk of film defects, which results in
- dose dumping.
- Hole Size is critical in the case of Elementary osmosis.
- Drug release from the osmotic systems is affected to some extent by the presence of
- food.
- Retrieval of therapy is not possible in the case of unexpected adverse events.
- The rapid development of tolerance (4).

### Osmosis

Osmosis functions as the mechanism through which a solvent moves from a region of lower solute concentration to one of higher concentration across a semipermeable membrane. This process plays a crucial role in controlling drug delivery systems. The osmotic pressure, generated by the influx of fluid from the external environment into the dosage form, regulates the release of drugs from osmotic devices. The rate of drug delivery from osmotic pumps is directly linked to the osmotic pressure induced by the absorption of fluids by osmogens. Osmotic pressure, a colligative property of solutions, remains unaffected by the number of solute particles present, making the release rate of drugs from osmotic dispensing devices reliant on factors such as solubility, molecular weight, and activity coefficient of the solute (osmogen) (5).

### Principle

Osmotic pressure governs osmotic drug delivery systems, as it's a colligative property reliant on solute concentration. Solutions of the same solvent and solute display osmotic pressure proportional to their concentrations, ensuring a steady influx of water and a consistent zero-order release rate for drugs. The release rate hinges on core osmotic pressure and drug solubility, making these systems ideal for moderately water-soluble drugs. Osmotic pressure varies with temperature and concentration, a relationship described by a specific equation (6).

$$\pi = n^2 RT$$

Where,

$\pi$  = osmotic coefficient

$n^2$  = molar concentration of solute in the solution

R = gas constant

T = Absolute temperature

### Classification of Osmotic Drug Delivery System

Osmotic drug delivery devices in general can be divided into two categories

A. Implantable

B. Oral

#### A. IMPLANTABLE OSMOTIC PUMPS

1. Rose-Nelson Pump

2. Higuchi Leeper Pump

3. Higuchi Theuwes pump

#### B. ORAL OSMOTIC PUMPS

1. Elementary Osmotic Pump

2. Push pull osmotic pump

3. Controlled porosity osmotic pump

4. Osmotic bursting osmotic pump

5. Monolithic osmotic systems

6. Multi-particulate osmotic pump

7. Sandwiched osmotic pump

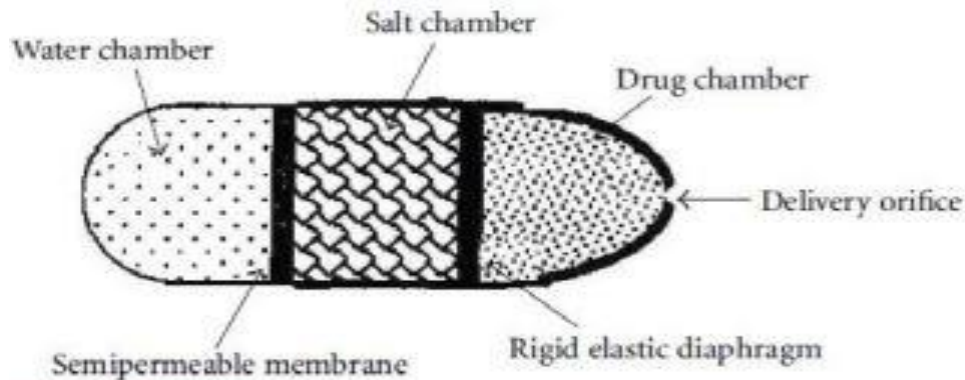
8. Liquid Oral Osmotic System (L-OROS)

9. OROS – CT (7).

## A. Implantable Osmotic Pumps

### 1. Rose-Nelson Pump

In 1955, Australian physiologists Rose and Nelson introduced the first osmotic pump, primarily aimed at delivering drugs to the gastrointestinal tract of sheep and cattle. The pump comprises a drug chamber with an orifice, a salt chamber containing excess solid salt an elastic diaphragm, and a water chamber. A rigid semi-permeable membrane separates the drug and water chambers. The osmotic pressure difference across the membrane drives water from the water chamber into the salt chamber, causing the volume of the salt chamber to expand. This expansion distends the latex diaphragm, thereby pushing the drug out of the device (8).



**Fig 1:** Rose Nelson pump

The pumping rate of the Rose-Nelson pump is given by the equation:

$$dm/dt = dv/dt * c$$

Where,

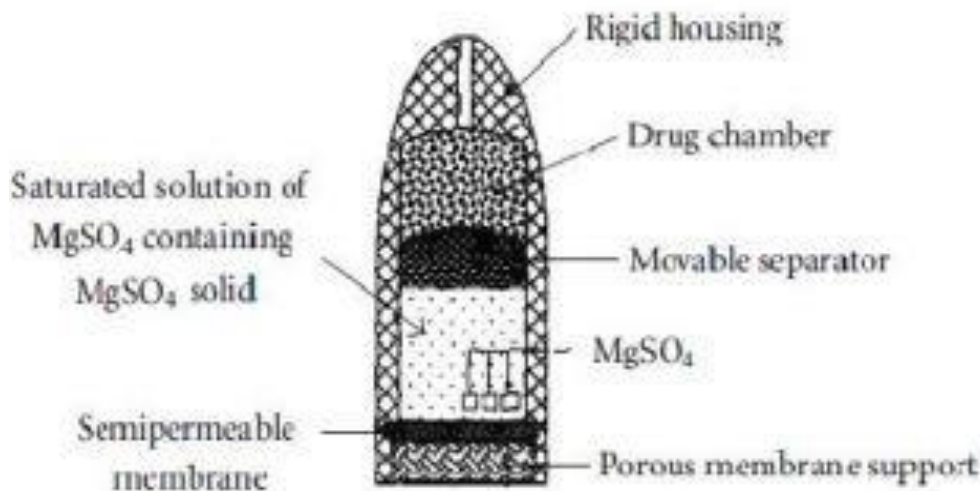
$dm/dt$  = Drug release rate.

$dv/dt$  = Volume flow of water into the salt chamber.

$c$  = Concentration of drug into drug chamber

### 2. Higuchi Leeper pump

This is the modified form of the Rose-Nelson pump which does not include a water chamber; instead, it relies on water imbibed from the surroundings for activation. This activation occurs when the pump is swallowed or implanted in the body. The driving force is generated by a chamber loaded with a saturated salt solution. The pump is prepared and then filled with the drug before being utilized (9).



**Fig 2:** Higuchi-Leeper pump

### 3. Higuchi- Theeuwes pump

In the early 1970s, Higuchi and Theeuwes devised a variant of the Rose-Nelson pump. This pump consists of a rigid outer semi-permeable membrane that regulates the release rate, encasing a solid salt layer. Inside this salt layer, there is an elastic diaphragm. Upon activation, water is osmotically drawn into the salt chamber, exerting pressure and pushing the drug out of the drug chamber (10).

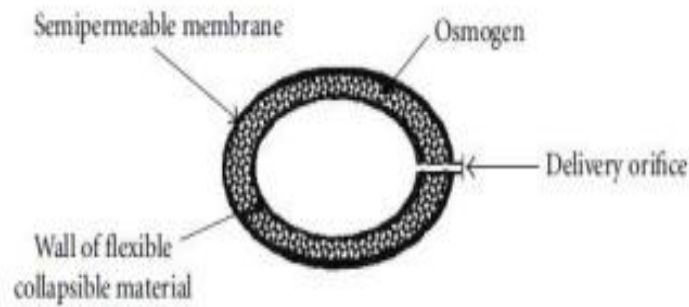


Fig 3: Higuchi Theeuwes pump

## B. Oral Osmotic Pumps

### 1. Elementary osmotic pump

This system, characterized by its simplicity in design, comprises an osmotic core containing the drug, possibly with an osmagent, enclosed by a semi-permeable membrane. Upon contact with aqueous fluids, the system absorbs water at a rate determined by the membrane's permeability and the osmotic pressure of the core formulation. This osmotic absorption leads to the formation of a saturated drug solution within the core, which is then released at a controlled rate through a delivery orifice in the membrane. While 60-80% of the drug is consistently released from the osmotic pump, there is an initial lag time as the system hydrates before zero-order delivery commences. This type of drug delivery is suitable for drugs with moderate water solubility (11,12).

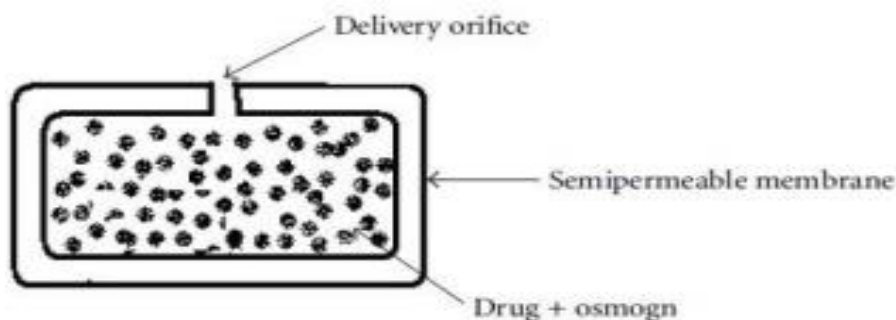


Fig 4: Elementary Osmotic Pump

### 2. Push-Pull osmotic pump (PPOP)

This system is an adaptation of the elementary osmotic pump, allowing for the constant delivery of poorly soluble drugs. It consists of two layers: an active pull layer containing the drug and a second push layer containing osmotically active (pharmacologically inert) components. The semi-permeable membrane surrounding the tablet only allows water to pass through, not the drug or any osmotic excipients. As water enters the tablet from the gastrointestinal tract, pressure builds in the osmotic layer, pushing the drug layer and facilitating drug release through a small orifice in the semi-permeable membrane coated on the drug side of the tablet. However, the expensive laser drilling technology required for creating the orifice in the drug compartment is a significant drawback (13,14).

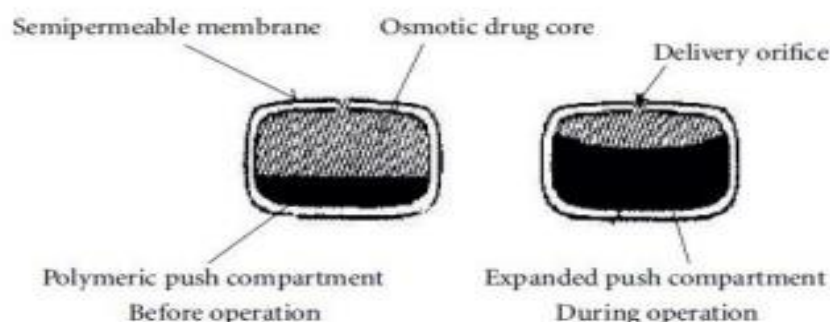


Fig 5: Push-pull osmotic pump (PPOP)

### 3. Controlled porosity osmotic pump (CPOP)

This system is a modified version of the elementary osmotic pump, facilitating the consistent delivery of poorly soluble drugs over time. It comprises two layers: an active pull layer housing the drug, and a second push layer containing osmotically active (but pharmacologically inert) components. Encased in a semi-permeable membrane, the tablet allows water from the gastrointestinal tract to permeate, increasing pressure within the osmotic layer. This pressure then propels the drug layer, prompting the controlled release of the drug through a minute orifice, meticulously drilled using costly laser technology. This reliance on expensive laser drilling poses a significant drawback (15).

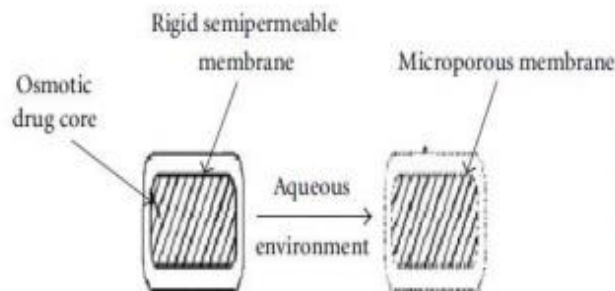


Fig 6: Controlled porosity osmotic pump

### 4. Bursting osmotic pump

This system resembles the elementary osmotic pump but lacks a delivery orifice. As gastrointestinal fluid permeates the core, pressure accumulates inside the pump until the wall ruptures, releasing the contents into the environment. It is useful for controlled drug release, as the rate of release can be adjusted by altering the thickness and composition of the semi-permeable membrane (16).

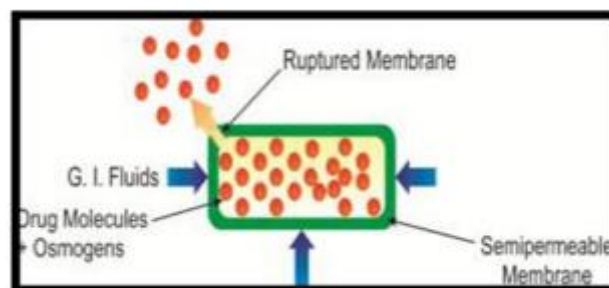


Fig 7: Bursting osmotic pump

### 5. Monolithic osmotic systems

A water-soluble drug is dispersed within a polymeric matrix and compressed into tablet form. Subsequently, the tablet is coated with a semi-permeable membrane. Upon contact with an aqueous environment, water permeates into the core, creating a saturated solution of the drug component. This generates osmotic pressure, leading to the rupture of the membrane surrounding the polymeric matrix containing the drug. Initially, this process occurs at the outer edge of the polymeric matrix and gradually progresses concentrically towards the inner portion of the matrix (17).

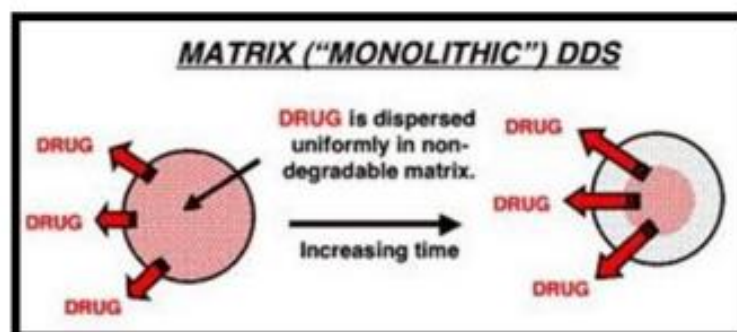


Fig 8: Monolithic osmotic system

### 6. Multi-particulate osmotic pump

In this method, pellets containing pure drugs along with an osmotic agent are coated with a semi-permeable membrane, such as cellulose acetate. Upon introduction into an aqueous environment, water is absorbed due to the osmotic pressure gradient, resulting in the formation of a saturated solution of soluble components. This causes the membrane to expand and form pores. The drug, along with other soluble components, is released through these pores, following zero-order kinetics (18).

### 7. Sandwiched osmotic tablet/Pump (SOT)

This system consists of a polymeric push layer positioned between two drug layers, each with its delivery orifice. When immersed in an aqueous medium, the central push layer containing swelling osmotic agents expands, causing the drug to be released from the two orifices in the drug layers located on opposite sides of the tablet. This design makes the System of Osmotic Delivery (SOTS) ideal for drugs that may potentially irritate the gastric mucosa locally (19).

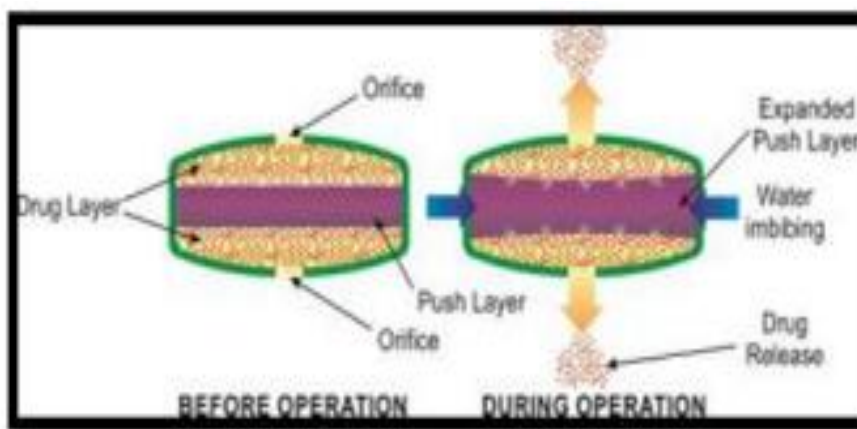


Fig 9: Sandwiched osmotic tablet

### 8. Liquid oral osmotic system (L-OROS)

The Delayed Liquid Bolus Delivery System is a type of Liquid OROS controlled release system specifically engineered to administer drugs in liquid formulations. Within this system, the liquid active pharmaceutical ingredient (API) formulation is encapsulated in either a soft or hard gelatin capsule. Surrounding the capsule are layers including a barrier layer, an osmogen layer, and a semi-permeable membrane, with a delivery orifice created through these layers. Upon contact with an aqueous environment, water absorption occurs, leading to the buildup of hydrostatic pressure inside the system. This pressure ultimately forces the liquid formulation to breach the hydrated gelatin capsule shell at the delivery orifice. The Delayed Liquid Bolus Delivery System offers controlled delivery of liquid drug formulations and is available in two configurations: L-OROS hard cap and L-OROS soft cap (20).

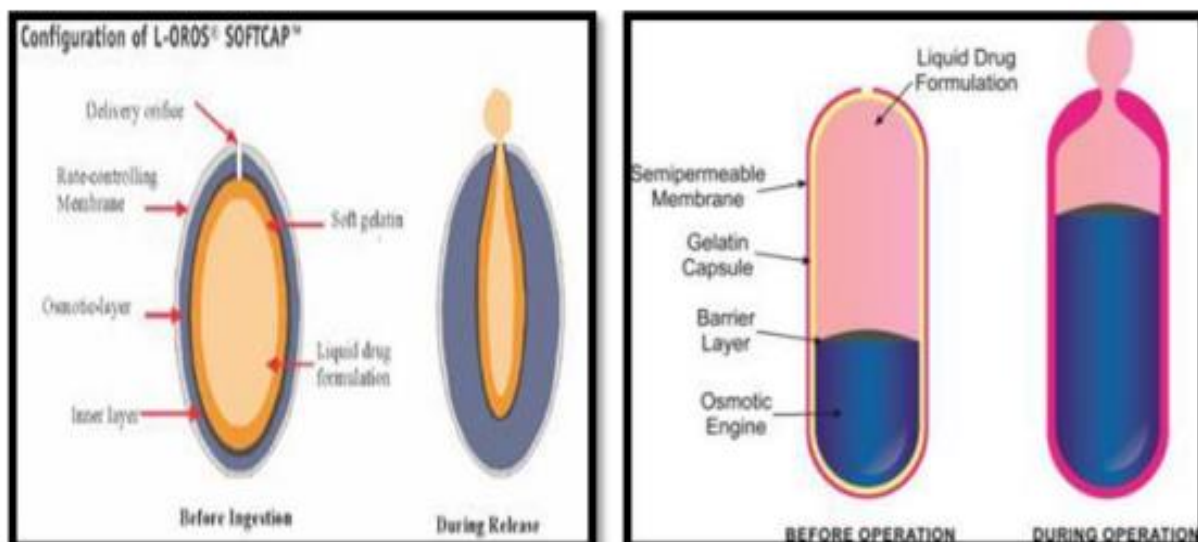


Fig 10: Liquid OROS

### 9. Colon targeted oral osmotic system (OROS-CT)

This system comprises 5-6 units of push-pull enteric-coated tablets enclosed within a hard gelatin capsule, designed for precise drug delivery to the colon. Upon contact with gastrointestinal fluids in the stomach, the gelatin capsule dissolves, while the enteric coating shields the units from these fluids. As the system progresses into the intestine, the enteric coating dissolves, allowing water to permeate into the core. This triggers swelling of the push compartment, facilitating the controlled release of the drug from the drug layer (21).

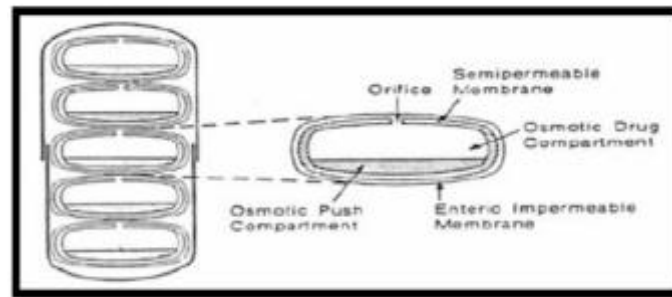


Fig 11: Colon targeted oral osmotic system

#### Basic components of the osmotic system

**a. Drug:** Osmotic systems are ideally suited for drugs with short biological half-lives and those requiring prolonged treatment. Various medications like DiltiazemHCl, Carbamazepine, Metoprolol, Oxprenolol, and others are formulated using osmotic delivery for this purpose.

**b. Wicking agent:** Wicking agents, either swellable or non-swellable, possess physiosorption capability with water, loosely adhering solvent molecules via Van der Waals interactions. They facilitate water transport within tablet cores, creating channels or increased surface area networks. Suitable materials include colloidal silicon dioxide, kaolin, titanium dioxide, alumina, niacinamide, sodium lauryl sulfate (SLS), low-weight polyvinylpyrrolidone (PVP), m-pyrol, bentonite, magnesium aluminum silicate, polyester, and polyethylene. Non-swellable wicking agents include SLS, colloidal silica, and PVP.

**c. Semipermeable membrane:** The selection of the polymeric membrane is crucial for osmotic drug delivery systems. The membrane must be impermeable to the drug and other components in the compartments, inert, and maintain dimensional integrity to ensure a constant osmotic driving force during drug delivery. Any polymer permeable to water but impermeable to solute can serve as a coating material in osmotic devices. Examples include cellulose esters like cellulose acetate, cellulose acetate butyrate, cellulose triacetate, ethyl cellulose, and Eudragits.

**d. Pore-forming agent:** Pore-forming agents induce the formation of micro-porous membranes. These membranes may be created in situ by the leaching of pore-formers during system operation. Pore-formers can be either inorganic or organic, solid or liquid. Examples include alkaline metal salts like sodium chloride, sodium bromide, potassium chloride, potassium sulfate, and potassium phosphate, alkaline earth metals such as calcium chloride and calcium nitrate, carbohydrates like sucrose, glucose, fructose, mannose, lactose, sorbitol, and mannitol, as well as diols and polyols such as polyhydric alcohols, polyethylene glycols, and polyvinylpyrrolidone.

**e. Plasticizers:** The selection and quantity of plasticizers in coating membranes are vital in osmotic system formulation. They alter the viscoelastic properties of polymers, influencing the permeability of polymeric films. Various plasticizers include:

- Polyethylene glycols
- Ethylene glycol monoacetate
- Diacetate - for low permeability
- Triethyl citrate
- Diethyl tartrate or Diacetyl - for more permeable films

**f. Osmotic agent:** These compounds, also termed osmogens, generate osmotic pressure within the system. In cases where the drug has low solubility, it exhibits zero-order release but at a slow pace. To accelerate the release rate, osmotic agents are incorporated into the formulation. These agents establish a substantial osmotic pressure gradient within the system, thereby enhancing the drug release rate. Some of the commercially used osmotic agents:

- Sodium chloride
- Fructose

- Sucrose
- Potassium chloride.

**g. Flux regulators:** Delivery systems can manipulate fluid permeability by incorporating flux-regulating agents. Hydrophilic substances like polyethylene glycols (300 to 6000 Da), polyhydric alcohols, and polyethylene glycols enhance flux, while hydrophobic materials like phthalates with alkyl or alkoxy groups (e.g., diethyl phthalate or dimethoxyethylphthalate) reduce flux. Insoluble salts or oxides, which are water-impermeable, can also serve this purpose.

**h. Coating solvent:** Solvents suitable for creating polymeric solutions used in manufacturing osmotic device walls are inert and do not harm the core, wall, or other materials. Typical solvents include methylene chloride, acetone, methanol, ethanol, isopropyl alcohol, butyl alcohol, ethyl acetate, cyclohexane, carbon tetrachloride, and water. Solvent mixtures like acetone-methanol (80:20), acetone-ethanol (80:20), acetone-water (90:10), methylene chloride-methanol (79:21), and methylene chloride-methanol-water (75:22:3) can also be utilized (22).

## 2. FORMULATION OF OSMOTIC CONTROLLED DRUG DELIVERY SYSTEM

The osmotic core tablets were prepared by the wet granulation method. The granules were prepared by the non-aqueous (IPA) granulation technique. Lornoxicam and all the excipients previously passed through a no. #60 sieve. Then, Lornoxicam was mixed with all the excipients except the binding and solubilizing agents as per the formulas given in Table 1-2. The blend was mixed for 10 minutes in a polybag and later, the mixture was granulated with a PVP K-30 (binder) in isopropyl alcohol (IPA) (solvent for wet granulation) and wetting/solubilizing agents. The resulting wet mass was passed through a no. #25 sieve and the granules were dried at 50 °C for 15 minutes to obtain a loss on drying (LOD) value between 1% and 1.2%, after which they were passed through a no #30 sieve and compressed using a tablet machine (Rimek mini press-II, Gujrat, India) (23).

### EVALUATION

The evaluation parameters are as follows

- 1) **Hardness:** Tablet diameter & crushing strength of randomly selected tablets were determined using a Schleuniger tablet hardness tester.
- 2) **Friability test:** From each formulation, 20 tablets were placed in a friability (Roche friabilator) and subjected to rotations for 4 minutes. The tablets were then redusted and reweighed. The friability was calculated as a percentage of weight loss.
- 3) **Effect of pH:** These are done to see the effect of pH on the development of formulation so an in vitro study is carried out in different media.
- 4) **Effect of osmotic pressure:** A release mechanism study is carried out at different osmotic pressures to see its effect on formulation.
- 5) **In-vitro evaluation:** In vitro, the release of drug from an oral osmotic system is by conventional USP paddle & basket type of apparatus. Dissolution media is generally distilled water as well as simulated gastric fluid (for first 2-4 h) and intestinal fluids (for subsequent hours) used the standard specifications, which are as follows for oral controlled drug delivery systems are equivalently applicable for oral osmotic pumps (24).

## 3. SUMMARY

In osmotic delivery systems, osmotic pressure delivers the driving force for drug release. Increasing pressure inside the device from water imbibition causes the drug to release from the factors at the delivery site. Controlled delivery through osmotic systems also reduce the side-effect profile by moderating the blood plasma peaks typical of conventional (e.g., instant release) dosage forms. Furthermore, since effective plasma levels are maintained longer in osmotic systems, avoidance of trough plasma levels over the dosing interval is possible.

Though, a complex manufacturing process and higher cost compared with conventional dosage forms limit their use. Therefore, most of the currently marketed products are based on drugs used in long-term therapies for diabetes, hypertension, attention-deficit disorder, and other chronic disease states.

Besides oral osmotic delivery systems, implants that work on osmotic principles are auspicious for delivery of a wide variety of molecules with a precise rate over a long period of time. Further, with the discovery of newer and potent drugs by the biotechnology industry, the need to deliver such compounds at a precise rate certainly will pave the way for osmotic delivery systems to play an increasingly important role in drug delivery.



#### 4. CONCLUSION

In the osmotic delivery system, the driving force for drug release is provided by osmotic pressure. As water enters the dosage form, pressure inside increases, prompting the release of the drug. One of the major advantages of this system is its ability to precisely control zero-order or other patterned release over an extended period. Over time, osmotic drug delivery has undergone various advancements and improvements. While it is considered a slightly more expensive drug delivery system, its ability to provide a consistent rate of drug release has contributed to its acceptance in the pharmaceutical industry.

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