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# OSMOTICALLY CONTROLLED DRUG DELIVERY SYSTEM-A NOVEL APPROACH

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**Keywords:**

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## ABSTRACT

Osmotically controlled drug delivery systems (OCDDS) are most promising systems for controlled drug delivery. Osmotically controlled drug delivery systems utilize osmotic pressure for controlled delivery of active agents. Various patents are available for osmotic drug delivery system like Rose and Nelson pump, Higuchi Leeper pump, Higuchi Theeuwes pump, Elementary osmotic pump etc. Various techniques available for preparation of OCDDS include push pull osmotic pump, Osmotic bursting osmotic pump, Liquid OROS, Telescopic capsule for delayed release, OROS-CT (colon targeting), and Sandwiched osmotic tablet system.These systems can be used for systemic as well as targeted delivery of drugs. Drug delivery from these systems, to a large extent, is independent of physiological factors of GI tract. Release of drug from formulation is depends on various formulation factors such as solubility of drug, osmotic pressure generated in the system, size of the drug delivery orifice, nature & thickness of rate controlling membrane. The present review article mainly focus on the basic components of osmotically controlled drug delivery system, various factors governing drug release from these systems and types of osmotically controlled drug delivery systems.

## INTRODUCTION

### Introduction to Osmotic Drug Delivery System

In recent years, great attention has been dedicated on the development of novel drug delivery systems (NDDS). The reason for this is relatively low development cost and time required for introducing NDDS as compared to the development of a NCE. In the form of NDDS, an existing drug molecule can get a 'new life' thus, increasing its market value, competitiveness and patient life. Amongst the various NDDS available in market per oral controlled release (CR) system hold the major market share because of their obvious advantages like ease of administration, reduced dosing frequency and better patient compliance Controlled release (CR) dosage forms are designed to release drug in vivo according to predictable rates that can be verified by in-vitro measurements.

Osmotic devices are most promising strategy based system for controlled drug delivery. They are among the most reliable controlled drug delivery system and could be employed as oral drug delivery systems or implantable device. Osmosis is an aristocratic bio phenomenon, which is exploited for development of delivery systems with every desirable property of an ideal controlled drug delivery system. Osmotic system utilizes the principles of osmotic pressure for delivery of drug.

The first osmotic effect was reported by Abbe Nollet in 1748. Later in 1877, Pfeffer performed an experiment using semi-permeable membrane for separation of sugar solution from pure water. Osmotic pressure is used as driving force for release the drug in controlled manner for long period. Osmotic drug delivery has come long way since, Australian pharmacologist Rose and Nelson developed an implantable osmotic pump introduced in 1955, oral osmotic dosage form came in 1972 when Theuwes invented elementary osmotic pump. [(1)] Osmotic tablet worked on the principle Osmosis i.e. movement of water across a selectively permeable membrane driven by a difference in osmotic pressure across the membrane. [(2)] It is driven by a difference in solute concentrations across the membrane that allows water, but rejects most solute molecules or ions.

Development of osmotic drug delivery systems was founded by Alza Corporation of the USA (now merged with Johnson & Johnson, USA) and it holds major number of the patents and also markets several products based on osmotic principle. The first and most important osmotic delivery system patent (U.S. Patent 3,845,770) assigned to Alza in 5 November 1974 and covering Theeuwes original elementary osmotic pump design. Indomethacin (Osmosin®) and Phenyl Propanolamine (Acutrim®) are the first two marketed osmotic based products. [(3)]

**Osmotic pumps offer following advantages [4,5]**

The following advantages have contributed to the popularity of osmotic drug delivery systems

1. The delivery rate of zero order is possible with osmotic system.
2. Delivery may be delayed or pulsed.
3. Higher release rates are possible with osmotic system compared with conventional diffusion-controlled delivery system.
4. The release rate of osmotic system is highly predictable.
5. For oral osmotic system, drug release is independent to gastric pH and hydrodynamic condition.
6. The release from osmotic system is minimally affected by presence of food in gastrointestinal tract.
7. A high degree of in vivo-in vitro correlation is obtained in osmotic system.
8. Improve patient compliance with reduced frequency.

**Osmotic pumps offer following disadvantages.**

1. Dose dumping, if coating is not proper
2. Rapid development of tolerance
3. Special equipment is required for making an orifice in the system
4. Residence time of the system in the body varies with the gastric motility and food intake
5. Hypersensitivity reaction may occur

**Need for developing osmotic drug delivery system:**

1. In order to reduce dose
2. To decrease dose related side effects
3. To minimize dose related side effects
4. To provide control release &Increase patient compliance

**Mechanism of osmosis**

Core material contain water soluble osmotically active agent and blended with water soluble or insoluble drug, additives and coating has been carried out which functions as semi permeable membrane. This semipermeable membrane only permeable to water, initial penetration of water dissolves the critical part of the core, resulting in development of an osmotic pressure difference across the device delivers a saturated volume equal to the volume of water uptake through the membrane. Initial lag time (per hour) during which delivery rate increases to its maximum value, drug release is zero order, till all solid material is dissolved.

The relation between Osmotic pressure (Π) and the concentration of non-electrolyte is given for dilute solution which may be assumed to exhibit ideal behaviour by the Van't Hoff equation, membrane.

ΠV = n 2 RT

Where V = is the volume of solution.

n 2 = is number of moles of solute.

T = thermodynamic temperature and

R = is the gas constant.

**Principle of osmosis**

Osmosis can be defined as the net movement of water across a selectively permeable membrane driven by a difference in osmotic pressure across the membrane. It is driven by a difference in solute concentrations across the membrane that allows passage of water, but rejects most solute molecules or ions. Osmotic pressure is the pressure which, if applied to the more concentrated solution, would prevent transport of water across the semi permeable membrane. Vant Hoff identified an underlying proportionality between osmotic pressure, concentration and temperature. He revealed that osmotic pressure is proportional to concentration and temperature and the relationship can be described by following equation.

Π = Ø c RT

Where, p = Osmotic pressure

Π = osmotic coefficient

c = molar concentration

R = gas constant

T = Absolute temperature

Osmotic pressure is a colligative property, which depends on concentration of solute that contributes to osmotic pressure. Solutions of different concentrations having the same solute and solvent system exhibit an osmotic pressure proportional to their concentrations. Thus a constant osmotic pressure, and thereby a constant influx of water can be achieved by an osmotic delivery system that results in a constant zero order release rate of drug [5]

**Historical aspects of osmotic system**

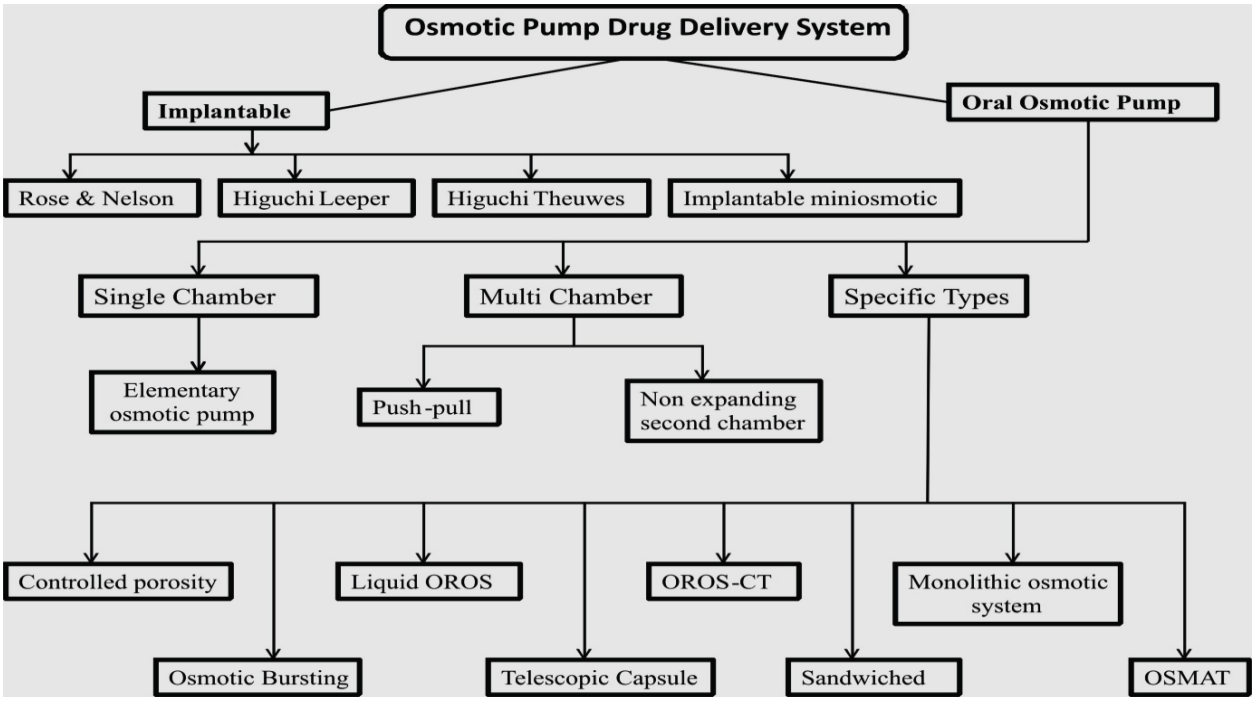
About 75 years after discovery of the osmosis principle, It was first used in the design of drug delivery systems [6]. Rose and Nelson, the Australian scientists, were initiators of osmotic drug delivery. In 1955, they developed an implantable pump, which consisted of three chambers a drug chamber; a salt chamber contains excess solid salt, and a water chamber.

The drug and water chambers are separated by rigid semi permeable membrane. The difference in osmotic pressure across the membrane moves water from the water chamber into the salt chamber. The design and mechanism of this pump is comparable to modern push pull osmotic pump. The major disadvantage of this pump was the water chamber, which must be charged before use of the pump. The pumping rate of this push-pull pump is given by the equation.

$$dM/dt = dV/dt \times c$$

In general, this equation, with or without some modifications, applies to all other type of osmotic systems. Several simplifications in Rose-Nelson pump were made by Alza Corporation in early 1970s. The Higuchi-Leeper pump is modified version of Rose- Nelson pump. It has no water chamber and the device is activated by water imbibed from the surrounding environment. The pump is activated when it is swallowed or implanted in the body. It has a salt chamber containing a fluid solution with excess solid salt. Recent modification in Higuchi-Leeper pump accommodated pulsatile drug delivery. The pulsatile release was achieved by the production of a critical pressure at which the delivery orifice opens and releases the drug .[7] This pump comprises a rigid, rate controlling outer semi permeable membrane surrounding a solid layer of salt coated on the inside by an elastic diaphragm and on the outside by the membrane. In use, water is osmotically drawn by the salt chamber, forcing drug from the drug chamber. [8]

**Classification of osmotic drug delivery system [9]**



**Implantable**

1. The Rose and Nelson Pump
2. Higuchi Leeper Pump
3. Higuchi Theuwes pump
4. Implantable Mini osmotic pump

**Oral osmotic pump**

1. Single chamber osmotic Pump tablet:
    - Elementary osmotic pump tablet (EOP)
2. Multilayer osmotic pump tablet:
    - Push- pull osmotic pump tablet
    - Sandwiched Osmotic tablet
3. Specific types

- Controlled porosity osmotic pump tablet(CPOP)
- Colon targeted oral osmotic system(OROS-CT)
- Asymmetrical membrane osmotic tablet
- Osmotically Rupturable tablet
- Liquid oral osmotic system(L-OROS)
- Effervescent osmotic tablet(EOT)
- Self-emulsified osmotic tablet
- Monolithic osmotic tablet(MOT)
- Osmotic pellet

**Implantable Osmotic Drug Delivery System**

Osmotic principles have been applied to human parenteral therapy, resulting in the development of the DUROS® implantable osmotic drug delivery system. These systems allow drug delivery for site-specific as well as systemic use for delivery periods of days to 1 year. [(10)] All materials in the DUROS system were selected for their biocompatibility and suitability for implant use. The drug-contacting materials are also screened for compatibility with the drug and the specific drug formulation excipients. Radiation sterilization (gamma) may be utilized to sterilize the final drug product. If the drug formulation cannot bear sterilizing doses of radiation, then a DUROS subassembly is radiation sterilized, and the drug formulation is added in a final aseptic operation. Hence, the materials in the DUROS system were also screened for their ability to withstand sterilizing doses of radiation.

**Oral osmotic drug delivery systems**

Oral route is the most popular route of administration of drugs in the body, most of the osmotic systems are developed for oral drug delivery. It is possible to deliver drugs at zero-order release rate, independent of its gastric pH and hydrodynamic conditions by osmotically controlled drug delivery systems. The oral osmotic pump are developed by coating the core tablet with the semi permeable membrane with an orifice or coat containing some leachable material which form In-situ pore for the controlled delivery of the drug. Osmotic tablets are orally active osmotically driven systems (OODS). Elementary osmotic pump was first introduced, but with time number of advances occurs in OODS. Following are different osmotic system and Special technology.

**A. Elementary Osmotic Pump Tablet (EOP)** [11, 12, 13, 14]

Theuwes invented elementary osmotic pump in 1972 (Fig.1). EOP consists of single-core system i.e. simple single layer osmotic core tablet surrounded by non-biodegradable coat having orifice (size varies from 0.5 to.1.5 mm). The researchers developed different drilling approaches like mechanical drilling, laser drilling (CO2laser beam with output wavelength of 10.6µ) which offered excellent reliability and indentation made in core tablets by using modified punches having needle on upper punch. EOP required external drilling.

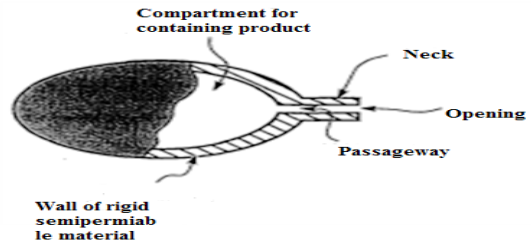



**Figure 1: Theuwes design of elementary osmotic pump (U.S. Patent 3,845,770)**

**B. Multilayer Osmotic Pump Tablet**

The osmotic system consists of multiple layers for controlling predetermined release pattern. Multilayer Osmotic Pump Tablet can be easily used for both water insoluble and soluble drug. Following are different multilayer osmotic system,

**1. Push Pull Osmotic Tablet** [15, 16, 17]

Push pull osmotic tablet (Fig. 2) characterized by swellable layer which pull the drug from osmotic pump. It is a bilayer tablet coated with a semi-permeable membrane. The upper compartment contains the drug and is connected to the outside environment via a small delivery orifice. Carbopol (around 20-40% wt of the tablet) is most commonly used polymer in push layer. This system also have disadvantage of localized release and higher cost.

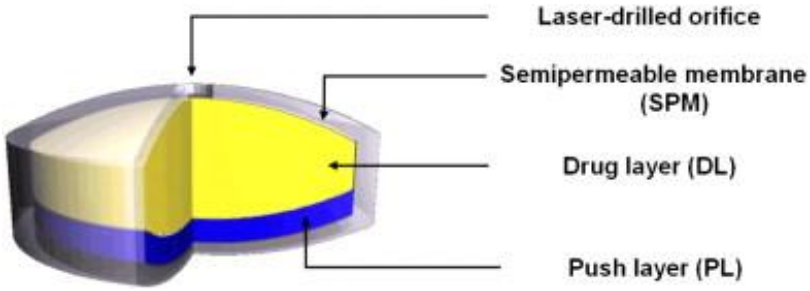



**Figure 2: Push pull osmotic tablet**

**2. Sandwiched Osmotic Tablet** [18]

Sandwiched osmotic tablet composed of polymeric push layer, sandwiched between two drug layers with two delivery orifices. When placed in the aqueous environment, the middle push layer, containing the swelling agents, swells and the drug is released from the delivery orifices. Drug is released from the two orifices situated on the opposite sides of the tablet and thus these pumps can be suitable for the drugs prone to cause local irritation of the gastric mucosa, Fig. 3.

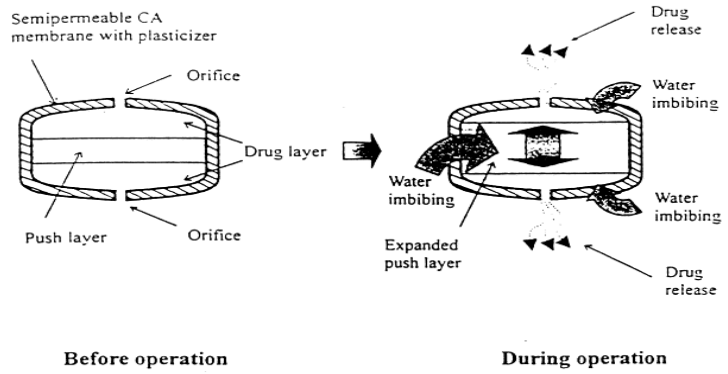



**Figure 3: Sandwiched osmotic pump**

**C. Controlled Porosity Osmotic Pump Tablet (CPOP)** [19]

A controlled porosity osmotic pump based drug delivery system consist water soluble pore forming agents incorporated in semi-permeable membrane. The membrane is accomplished by the use of different channelling agents in the coating. The drug release is achieved by the pores,which are formed in the semipermeable wall in situ after administration. (Fig 4).

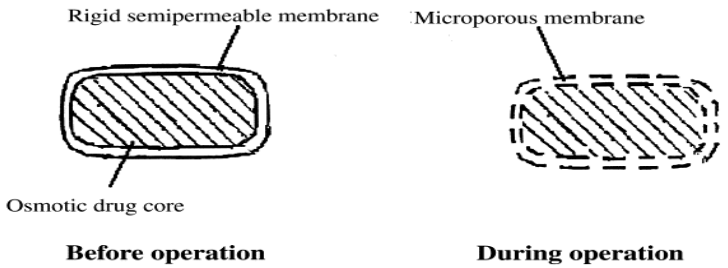



**Figure 4: Controlled porosity osmotic pump**

**D. Colon Targeted Oral Osmotic System (OROS-CT)** [20, 21]

OROC-CT is non-disintegrating osmotically driven tablets that release the drug specifically in colon (Fig. 5). OROS-CT surrounded by enteric coating which 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.

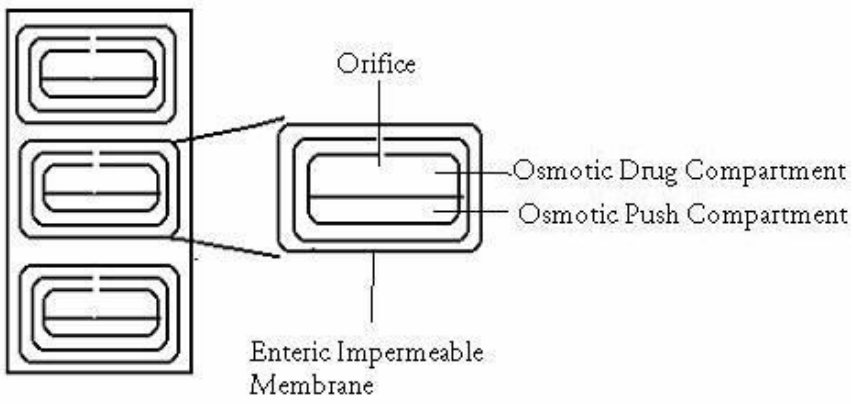



**Figure 5: Colon targeted oral osmotic system**

**E. Asymmetrical Membrane Osmotic Tablet** [22, 23, 24]

Asymmetric membrane capsules consist of a drug containing core surrounded by a membrane which has an asymmetric structure i.e. it has a relatively thin, dense region supported on a thicker, porous region. The capsule wall is made from a water insoluble polymer such as cellulose acetate unlike a conventional gelatin capsule; the asymmetric membrane capsule does not dissolve immediately but provides prolonged release of the active ingredient incorporated in the capsule.

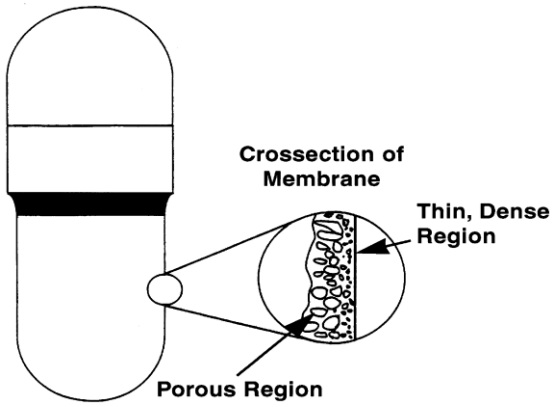



**Figure 6: Asymmetric membrane capsule**

**F. Osmotically Rupturable Tablet** [25]

A controlled-release delivery system utilizing an osmotic bursting mechanism was invented by Baker. The system surrounded by a semipermeable membrane and when placed in an aqueous environment, osmotic components imbibes water into the systems result into swelling, swelling continue until the membrane ruptured and released the active compound to the outside environment. Once the systems ruptured, drug was released by osmotic pumping and diffusion mechanisms through the ruptured area.

**G. Liquid-oral osmotic system (L-OROS)** [26]

Liquid OROS are designed to deliver 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.

Each of these systems includes a liquid drug layer, an osmotic engine or push layer and a semi-permeable membrane coating. When the system is in contact with the aqueous environment water permeates across the rate controlling membrane and activate 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 through the delivery orifice.

**H. Effervescent Osmotic Tablet** [27]

Drugs which are poorly soluble at low pH may precipitate at the gastric pH and block the delivery orifice, thus affecting the functioning of the osmotic pump. An effervescent compound, such as potassium bicarbonate can be incorporated to overcome the problem. The bicarbonate reacts with the acid in the exterior environment generating carbon dioxide. The expansion of the gas dispenses the precipitated drug and aids in rapid absorption of the drug and preventing the blockage of the orifice (Hou et al.) studied the effervescent osmotic pump tablet of Traditional Chinese Medicine Compound Recipe (TCMCR) named as Fuzilizhong. Sodium chloride and sodium hydrogen carbonate are most commonly used osmogen in EOT.

**I. Self-Emulsified Osmotic Tablet** [28, 29]

Self –Emulsified osmotic tablets are useful for new chemical entities exhibit poor aqueous solubility and present a major challenge to modern drug delivery system, because of their low bioavailability. The Self-emulsifying osmotic pump tablet (SEOPT) has two outstanding features; it could improve the bioavailability by self-emulsifying drug delivery system

(SEDDS), control the release rate and make the plasma concentrations more stable. Self-emulsifying drug delivery systems (SEDDS) are usually used to improve the bioavailability of hydrophobic drugs

**J. Monolithic Osmotic Systems (MOS)** [30, 31]

The systems consist of uniformly dispersion of osmotically active therapeutic agents (drugs) in biocompatible polymeric matrices. The drug particles are encapsulated by polymers to form microcapsules throughout the matrix. These osmotic systems display zero-order drug delivery kinetics. The principal energy source leading the release of agents is osmotic pressure. When such a system is placed in an aqueous medium, the tablet imbibes water into the outer most layer of the dispersion at a rate dictated by permeability of the polymer. Water transport into the film continues until rupture of the drug-containing capsules occurs, after which time saturated drug solution is pumped through channels created by the rupture. This process repeats itself in a serial fashion until the system is exhausted of agent. Due to the osmotic functionality of these systems, reduction of the thermodynamic activity of water outside the system can proportionally reduce the release of agent.

**K. Osmotic Pellet** [32, 33]

Osmotic pellet is a new model of drug release by osmotic pumping and diffusion mechanism. Pellets coated with a semipermeable film developing pores created by the leaching of water-soluble compounds initially present in the coating. The model describes dynamically all the main processes occurring during release, i.e. the inflow of solvent driven by the difference in osmotic pressure across the coating film, dissolution of the drug, swelling of the pellet due to mass accumulation, the build-up of hydrostatic pressure inside the pellet, and the outflow of the dissolved drug through the pores. Drug release from a coated formulation can occur by diffusion through the film and pores in the film, or by convection through pores or micro-cracks present in the film. Drug release by diffusion from coated pellets along with osmotic pressure has been extensively studied and reported in the literature.

**Elementary osmotic pump (EOP)** [34]

Elementary osmotic pump works on the same mechanism as the impalatable pumps it is simplest possible form of osmotic pump as it does not require special equipment and technology .This device was further simplification of Higuchi – Theeuwes pump. EOP was developed in the year 1975 by Theeuwes . The EOP consist of single layered tablet core containing a water soluble drug with or without other osmotic agent. A semi permeable membrane surrounds the core of the tablet. When such a system is absorbed water from the

GIT enter 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 drug continues to be delivered but at a declining rate until the osmotic pressure between outside environment and saturated drug solution .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.

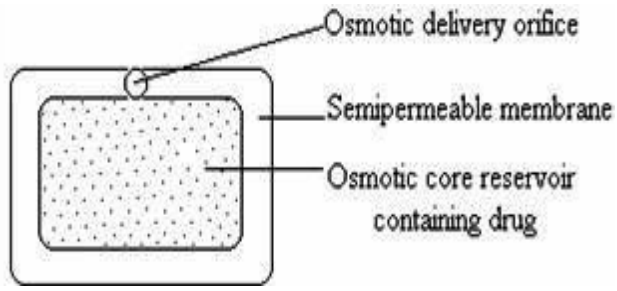



**Fig 7: Elementary osmotic pump**

**Basic components of osmotic systems** [35]

1) Drug

2) Osmotic Agent

3) Semi permeable Membrane

4) Plasticizers

5) Wicking agent

6) Pore forming agent

7) Flux regulators

8) Coating Solvent

**1)Drug**

All drugs are not suitable for osmotic system for prolong action .Which have short biological half-life>12 hr. Drug which have biological half-life in between 1-6 hrs. and which is used for prolonged cure of diseases are ideal applicant for osmotic systems .

**2) Osmotic Agent** [36]

Osmotic agents are usually ionic compounds consisting of either inorganic salts or hydrophilic polymers. Some osmotic agents that can be used for such systems are classified below. Different type of osmogents can be used for such systems are categorized as water-soluble salts of inorganic acids like magnesium chloride or sulphate, lithium, sodium, or potassium chloride; sodium or potassium hydrogen phosphate, water-soluble salts of organic

acids like sodium and potassium acetate, magnesium succinate, sodium benzoate, sodium citrate, sodium ascorbate; Carbohydrates like mannose, sucrose, maltose lactose, water-soluble amino acids and organic polymeric osmogents.

**3) Semi permeable Membrane**

Semipermeable membrane plays an important part of the osmotic drug delivery system .Therefore, the polymeric membrane selection is fundamental to osmotic delivery formulation. The membrane must possess certain performance criteria such as:

- Semi permeable membrane should be sufficient wet strength and water permeability
- Semi permeable membrane Should be biocompatible
- Semi permeable membrane Rigid and non-swelling
- Semi permeable membrane should be sufficient thick to withstand the pressure within the device.

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

| Sr. No. | Polymer | Water vapor transmission rates (g/100 $in^2$/24 hr./1mm thick film ) |
|---|---|---|
| **1** | Cellophane, polyethylene coated | 1.2 |
| **2** | Cellulose acetate | 40-75 |
| **3** | Ethyl cellulose | 75 |
| **4** | Ethylene propylene copolymer | 0.8 |
| **5** | Ethylene vinyl acetate | 1-3 |
| **6** | Methyl cellulose | 70 |
| **7** | Polyethylene | 0.5- 1.2 |
| **8** | Polypropylene | 0.7 |
| **9** | Polyvinyl alcohol | 100 |
| **10** | Polyvinyl chloride, cast | 10-20 |
| **11** | Polyvinyl chloride, excluded | 6-15 |
| **12** | Polyvinyl chloride, rigid | 0.7 |

**Table II: Examples of polymer used as semipermeable membrane** [39,40]

**4) Plasticizers**

Different types and amount of plasticizers used in coating membrane also have a significant importance in the formulation of osmotic systems. They can change viscoelastic behaviour of polymers and these changes may affect the permeability of the polymeric films. Some of the plasticizers used are as below:

- Polyethylene glycols
- Ethylene glycol monoacetate; and diacetate- for low permeability
- Tri ethyl citrate, Diethyl tartarate or Diacetin- for morepermeable film

**5) Wicking agent**

Wicking agents are help to increase the contact surface area of the drug with the incoming aqueous fluid. The use of the wicking agent help to enhance the rate of drug released from the orifice. The examples are colloidal silicon dioxide, PVP& Sodium lauryl sulphate.

**6) Flux regulators**

Flux regulators are used to regulate the permeability of the fluid .Hydrophilic substances such as polyethylene glycols (PEG 300 to 6000 Da), polyhydric alcohols, and polyalkylene glycols are used as flux enhancers.

**7) Pore forming agent**

These agents are particularly used in the pumps for poorly water soluble drugs also used in the development of controlled porosity or multiparticulate osmotic pumps. This pore forming agents cause the formation of micro porous membrane .The micro porous wall may be formed in situ by a pore-former by its leaching during the operation. The pore former are inorganic and organic solid/liquid in nature e.g. alkaline metal salts such as sodium chloride, sodium bromide, potassium chloride, potassium sulphate, potassium phosphate, alkaline earth metals such as calcium chloride and calcium nitrate, carbohydrates such as sucrose, glucose, fructose, mannose, lactose, sorbitol, mannitol and polyols such as polyvinyl pyrollidine.

**8) Coating Solvent[41]**

Solvents suitable for making polymeric solution that is used for manufacturing the wall of the osmotic device include inert inorganic and organic solvents that do not adversely harm the core, wall and other materials. The typical solvents include methylene chloride, acetone, methanol, ethanol, isopropyl alcohol, butyl alcohol, ethyl acetate, cyclohexane, carbon tetrachloride, water etc. The mixtures of solvents such as acetonemethanol (80:20), acetone-ethanol (80:20), acetonewater (90:10), methylene chloridemethanol (79:21), methylene chloridemethanol- water (75:22:3) etc. can be used.

**Factors affecting the release rate from EOP** [34]

There are following factors which should be considered while designing an EOP. These factors are also applicable to other osmotic drug delivery systems:

1. Membrane thickness
2. Osmotic pressure
3. Type of membrane and characteristics.
4. Solubility.
5. Size of the delivery orifice.
6. Use of Wicking agent.
7. Type and amount of plasticizer.

**1. Membrane thickness: -** A principle factor controlling the rate of penetration of water into the dispenser is the thickness of the membrane. The permeability of water into the membrane can be enhanced by the choice of a suitable type of the 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 achieve by varying the thickness of the membrane.

**2. Osmotic pressure:** -Rate of drug release from an Osmotic system is directly proportional to Osmotic Pressure of the core formulation. The osmotic pressure π directly affects the release rate. To achieve a zero-order release rate, it is essential to keep π constant by maintaining a saturated solute solution. Many times, the osmotic pressure generated by the saturated drug solution may not be sufficient to achieve the required driving force. In this case, other osmotic agents are added that enhance osmotic pressure. In order to achieve optimized and constant Osmotic Pressure in compartment Osmotic agent must be added to tablet.

**Table No 1: Some of the commercially used osmotic agents along with their osmotic pressure Compound / Mixture Osmotic pressure (atm).**

| Compound or mixture | Osmotic pump atmospheric pressure (atm) | Compound or mixture | Osmotic pump atmospheric pressure (atm) |
|---|---|---|---|
| Sodium chloride | 356 | Dextrose – Fructose | 450 |
| Fructose | 355 | Sucrose – Fructose | 430 |

| Compound or mixture | Osmotic pump atmospheric pressure (atm) | Compound or mixture | Osmotic pump atmospheric pressure (atm) |
|---|---|---|---|
| Potassium chloride | 245 | Mannitol – Fructose | 415 |
| Xylitol | 104 | Lactose - sucrose | 250 |
| Sorbitol | 84 | Lactose – Dextrose | 225 |
| Dextrose | 82 | Mannitol – Dextrose | 225 |
| Citric acid | 69 | Dextrose – Sucrose | 190 |
| Tartaric acid | 67 | Mannitol – Sucrose | 170 |
| Potassium phosphate | 105 | Mannitol - Lactose | 130 |
| Melanic acid | 117 | Lactose | 23 |
| Lactose – Fructose | 500 | Potassium sulphate | 38 |

1. **Type of membrane and characteristics:** Drug release from an osmotic system is largely independent of the pH and agitation intensity of GIT tract this is because of its selective water permeable membrane and effective isolation of dissolution process of drug core from the gut environment. The in– vivo release rate of the system is therefore independent of its position in the GIT, because the membrane in the osmotic system is semi permeable in nature any polymer that is permeable to water but impermeable to solute (drug, organic and inorganic ions) can be selected example include cellulose ester such as cellulose acetate, cellulose diacetate, cellulose triacetate, cellulose propionate, and cellulose ether such as ethyl cellulose and Eudragit. Among the cellulose polymer cellulose acetate membrane are mostly used because of its high water permeability characteristics and it can be adjusted varying the degree of acetylation of the polymer. The permeability of this membrane can be increased further by adding plasticizer to the polymer, which increases the water diffusion coefficient or hydrophilic flux enhancer which increases the water sorption of the membrane. A few example of hydrophilic flux enhancer are Polyethylene glycols300, 400, 600, 1500, 4000, and 6000

**Ideal Property of Semi Permeable Membrane**

The Semi Permeable Membrane must meet some performance criteria,

- The material must possess sufficient wet strength (-$10^5$) and wet modulus so as to retain its dimensional integrity during the operational lifetime of the device.
- The membrane exhibit sufficient water permeability so as to retain water flux rate in the desired range. The water vapour transmission rates can be used to estimate water flux rates
- The reflection coefficient and leakiness of the osmotic agent should approach the limiting value of unity. Unfortunately, polymer membranes that are more permeable to water are also, in general more permeable to the osmotic agent.
- The membrane should also be biocompatible.

**4. Solubility:** In the case of the EOP solubility is one of the most important factors affecting the drug release kinetics from the osmotic pumps. The drug with the solubility of ≤0.05 g/cm2 would release the drug ≥95% by the zero order kinetics. On other hand Zero order release rate would be slow according to the equation because of the small osmotic pressure and drug solubility .At the same time highly water soluble drugs (≥0.3 g/cm3) would be zero order for small percentage of the initial drug load .Thus the intrinsic water solubility of many drug might preclude them from incorporation in an osmotic pump of EOP design. Candidate drug for osmotic delivery should have solubility within the range of 50- 300 mg/ml.

**5. Size of the delivery orifice:** The orifice is one of the most important parts in the membrane for the drug release. The size of the orifice must be optimized in order to control the drug release from the osmotic system. In the case of a formulation delivery orifice the size must be smaller than the maximum size (Amax) to minimized the solute diffusion through the orifice .The hydrostatic pressure may not be relived because small seize of orifice may lead to deformation of the delivery system there resulting in unpredictable drug release.

Methods to create a delivery orifice in the osmotic tablet coating are:[42]

· Mechanical drill

· Laser drill: This technology is well established for producing sub-millimeter size hole in tablet. Normally CO2 beam (with output wavelength of 10.6μ) is used for drilling purpose

· Indentation that is not covered during coating process : Indentation made in core tablet by using modified punches having needle on upper punch.

· Use of leachable substances in the semipermeable coating: e.g. controlled porosity osmotic pump.

**6. Use of Wicking agent:** The wicking agents are those agents which help to increase the contact surface area of the drug with the incoming aqueous fluid. The use of the wicking agent help to enhance the rate of drug released from the orifice of the drug. The examples are colloidal silicon dioxide, PVP & Sodium lauryl sulphate.

**7. Type and amount of plasticizer:** In pharmaceutical industry coatings, plasticizers & low molecular weight diluents are added to modify the physical properties and improve film forming characteristic of polymers. The plasticizers can turn a hard and brittle polymer into a softer, more pliable material & make it more resistant to mechanical stress. The polymer can affect the permeability of the polymer films can result in the rate of change of drug release from the osmotic tablets.

**Evaluation parameters for osmotic tablet** [37, 38]

- **Visual inspection:**

Visual inspection of the film for smoothness, uniformity of coating, edge overage and luster

- **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 coating

- **Coat weight and thickness:**

The coat weight and thickness can be determined from depleted devices by following careful washing and drying of the film using standard analytical balance and screw guage.

- **Orifice diameter:**

The mean orifice diameter of the osmotic pump tablet can be determined by using scanning electron microscopy (SEM)

- **In vitro drug release:**[35]

The in vitro drug release rate of drug from osmotic system can be determined using diverse methodologies, conventional USP dissolution apparatus I & II .

**Table no 3: Marketed Product**

| Brand Name | API | Type | Marketed by |
|---|---|---|---|
| UT-15C | Treprostinil diethanolamine | SEOP | United therapeutics |
| LCP-Lerc | Lercanidipine | DOEOP | Osmotica |
| Cadura CRD | Doxazosin mesylate | PPOP | Alza/Pfizer |
| Oxycontin | Oxycodone | PPOP | Alza |
| Elafax XR | Valenfexine HCL | EOP | Phoenix |

| Brand Name | API | Type | Marketed by |
|---|---|---|---|
| Invega | Paliperidone | PPOP | Xian-Janssen |
| Volmax | Albuterol | EOP | GSK/Muro |
| Fortamet | Metformin/pioglitazone | SCOT | Andrax |
| Alto plus XR | Metformin | SCOT | Takeda |
| Dynacric CR | Isradipine | PPOP | Alza/Novartis |
| Jusnista | Hydromorphone | PPOP | J&J |
| Altoprev | Lovastatin | EOP | Andrex |
| Allegra D24 h | Fexofenadine | DOEOP | Osmotica |
| Topamax | Toperamate | PSOP | Alza |
| Mildugen D | Astemizole | DOEOP | Osmotica |
| Alpress LP | Prazosin | PPOP | Pfizer |
| Acutrim | Phenylpropanolamine | EOP | Alza |
| Glucotrol XL | Glipizide | PPOP | Pfizer |
| Minipress XL | Prazocin | EOP | Alza |
| Efidac 24 | Chlorpheniramine maleate | EOP | Alza |

## CONCLUSION

In osmotic delivery systems, osmotic pressure provides the force for drug release. Osmotic pressure increases inside the dosage form water movement causes the drug to release from the system. The main advantages include precise control of zero-order release over an extended time Controlled delivery through osmotic systems also may reduce the side-effect profile by controlling the blood plasma peaks typical of conventional dosage forms. Also, efficacious plasma levels are maintained for longer period in osmotic systems. Once-daily formulations based on osmotic principles are playing an increasingly important role in improving patient compliance. Therefore, most of the currently marketed products are generated on drugs used in long-term therapies for diabetes, hypertension, attention-deficit disorder, and other chronic disease states. The osmotic drug development is somewhat costly type of drug delivery system but it provides a good rate of drug release. Which tends to increase its acceptance in pharmaceutical world besides oral osmotic delivery systems, implants that work on osmotic principles are promising for delivery of a wide variety of molecules with a precise rate over a long period of time.

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