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Review Article

Osmotic drug delivery systems: A review

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ABSTRACT

Oral route is most predominant route for administration of drugs. Recent Novel drug delivery systems are developed in oral route to improve the patient compliance and reduce adverse effects. Osmotic controlled drug delivery systems are a type of Novel drug delivery systems which utilize osmotic pressure for controlled delivery of active agent(s). The release of drug(s) from osmotic systems is independent of gastric pH & gastric motility. The release of drug(s) from osmotic systems is affected by various formulation factors such as osmotic pressure of the core component(s), solubility and size of the delivery orifice, and nature of semi permeable membrane. Different types of osmotic systems have been developed implantable & oral. This review focuses on types of Osmotic drug delivery systems, factors affecting release of drug and available drugs in market.

Key Words: Controlled drug delivery systems, push pull osmotic drug delivery systems

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INTRODUCTION

Oral drug delivery is the most widely utilized route of administration when compared to all the other routes that have been known for the delivery of drugs. The role of novel drug delivery system is to develop an optimized product that will be therapeutically effective with additional benefits such as

- Maintenance of constant blood levels within the therapeutic window
- Enhanced bioavailability
- Reduced inter patient variability
- Decreased dosing frequency
- Improved patient compliance
- Reduced side effects

Research has led to development of novel drug delivery system among which osmotic controlled drug delivery system (OCDDS) utilize osmotic pressure for controlled delivery of drug. Drug delivery from these systems is independent of physiological factors of GI tract. Release of drug from the formulation is dependent on various formulation factors such as

- Solubility of drug
- Osmotic pressure gradient of the system
- Size of the delivery orifice
- Nature and thickness of rate controlling membrane (semi permeable membrane)

Zero order release rate is expected in OCDDS. (Release rate is independent on concentration of the drug). Drug release from OCDDS is independent of pH and hydrodynamic conditions of the body, because of the semi permeable nature of the rate-controlling membrane and the design of delivery orifice present in osmotic systems, drug dose is released in controlled pattern, so a high degree of *in vivo-in vitro* correlation is achieved. There are over 240 patented osmotic drug delivery systems.

Osmosis

Osmosis is the flow of water between two solutions separated by a semi-permeable membrane. The driving force is created by a difference in solute concentrations across the membrane that allows passage of water but not solute molecules or ions. Osmotic pressure is the pressure which, if applied to the more concentrated solution side would prevent inward flow of water across the semi permeable membrane.

The first osmotic effect was reported by Abbe Nollet in 1748, later in 1877, Pfeffer performed an experiment using semi-permeable membrane to separate sugar solution from pure water. He showed that the osmotic pressure of the sugar solution is directly proportional to the solution concentration and the absolute temperature. In 1886, 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.

$$\Pi = Ø\ c\ RT$$

Where, Ø = osmotic pressure, Π = osmotic coefficient, c = molar concentration, R = gas Constant, T = absolute temperature

ADVANTAGES:

- Improved patient compliance with reduced dosing frequency
- Prolonged therapeutic effect with uniform blood concentration
- Zero order release profile
- Drug delivery rate may be delayed or increased if desired
- Drug release is independent of gastric pH and hydrodynamic condition
- A high degree of in-vitro and in-vivo correlation *(ivivc)* is obtained in osmotic system

DISADVANTAGES:

- Expensive process in case of involvement of laser drilling technology
- Rapid drug tolerance
- Saturated solution of drug may cause local gastric irritation
- If coating process is not optimized properly there is a risk of film defects resulting in dose dumping
- Residence time of the system varies with the food intake and gastric motility which may create a problem especially for targeted drug delivery.
- Dose dumping may occur if the system is not well formulated.
- Retrieval therapy is difficult in case of dose dumping.

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

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

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

A. IMPLANTABLE OSMOTIC PUMPS

Rose-Nelson Pump: Australian pharmacologists Rose & Nelson first developed an implantable pump in 1955. It consists of three chambers drug, salt, water. The drug, salt and water chamber are separated by rigid semi permeable membrane. The difference in osmotic pressure on either side of the membrane moves water from the water chamber into the salt chamber. The salt chamber increases in volume because of this water inflow, which pushes the diaphragm separating the salt and drug chambers, there by pumping drug out of the device. This design and mechanism of this pump is comparable to modern push-pull osmotic pump. The major disadvantage of this pump was the water chamber, must be charged before the use of the pump.

Higuchi-Leeper osmotic pump: It is a modified Rose-Nelson pump. It has no water chamber and the device is activated by water imbibed from the surrounding, the pump is activated when swallowed or implanted in the body, the driving force is created by chamber which is loaded with saturated salt solution. The pump is first prepared and then loaded with the drug prior to use.

Higuchi- Theeuwes pump: In the early 1970 Higuchi – Theeuwes developed a similar form of Rose Nelson pump. This pump comprises a rigid rate controlling outer semi permeable membrane, surrounding a solid layer of salt which in turn is surrounded on the inside by an elastic diaphragm and when activated, water is osmotically drawn by the salt chamber, forcing drug from the drug chamber.

B. ORAL OSMOTIC PUMPS

Elementary Osmotic Pump: which is simple in design, consists of an osmotic core consisting of drug with or without an osmagent coated with a semi permeable membrane. The system, after coming in contact with the aqueous fluids, absorbs water at a rate determined by the permeability of the membrane and osmotic pressure of core formulation. These osmotic imbibitions of water results in formation of a saturated solution of drug within the core, released at a controlled rate from the delivery orifice in the membrane. Though 60–80% of drug is released at a constant rate from EOP, a lag time is observed as the system hydrates before zero-order delivery from the system begins. Drugs having moderate water solubility are suitable for this type of drug delivery.

Push-Pull Osmotic Pump (PPOP): It is a modified form of elementary osmotic pump, delivery of poorly soluble drugs at a constant rate is possible this system. It consists of two layers an active pull layer containing the drug, and second push layer containing osmotically active (pharmacologically inert) components. The semi permeable membrane around the tablet is permeable only to water but not to drug or any osmotic excipients. As water from the gastrointestinal tract enters the tablet, pressure increases in the osmotic layer and pushes the drug layer, resulting in the release of drug through a small, laser-drilled orifice in the semi permeable membrane coated on the drug side of the tablet. Expensive laser drilling technology employed to drill the orifice in the drug compartment is a major disadvantage.

Controlled Porosity Osmotic Pump (CPOP): This system consist of core tablet coated with a semi permeable membrane containing leachable pore-forming agents, when CPOP comes in contact with the aqueous environment the water soluble component of outer coating dissolves and forms microspores in membrane and water diffuses inside the core through micro porous membrane, setting up an osmotic gradient and there by controlled release of the drug. Drug release rate depends on various factors like coating layer thickness, solubility of drug in tablet core. The gastric irritation problems are mostly reduced, as drug is released from the whole of the device surface rather from a single hole, additionally no complicated laser-drilling unit is required because the holes are formed *in-situ*.

Bursting Osmotic Pump: This system is similar to elementary osmotic pump except the delivery orifice is absent. As the GI fluid permeates into the core, pressure is built up inside the pump until the wall bursts and the contents are released into the environment. It can be employed for controlled release of drug, by varying the thickness and the nature of the semi permeable membrane the rate of drug release can be controlled.

Monolithic Osmotic Systems: Dispersion of water soluble drug is made in a polymeric matrix and compressed as tablet. Tablet is then coated with semi permeable membrane. When comes in contact with aqueous environment, the water penetrates into the core and forms a saturated solution of component which will generate osmotic pressure

which results in the rupturing of membrane of polymeric matrix surrounding the agent. Initially this process occurs at the outer part of the polymeric matrix, but gradually proceeds towards the inner portion of the matrix in a concentric manner.

Multi -Particulate Osmotic Pump: In this technique pellets containing pure drug with osmogen is coated with a semi permeable membrane for example. Cellulose acetate. When such a system is introduced into the aqueous environment water is imbibed due to the osmotic pressure gradient which leads to formation of saturated solution of soluble components, expansion of membrane and formation of pores. The drug along with other soluble components is released through the pores which follows zero-order kinetics.

Sandwiched Osmotic Tablet/Pump (SOT): It is comprised of polymeric push layer sandwiched between two drug layers with their respective delivery orifices. When placed in the aqueous medium the middle push layer containing the swelling osmotic agents swells and the drug is released from the two orifices of drug layers situated on opposite sides of the tablet and thus SOTS can be suitable for drugs prone to cause local irritation of the gastric mucosa.

Liquid OROS: Liquid OROS controlled release systems are specially designed to deliver drugs as liquid formulations. Liquid API formulation is present in a soft or hard gelatine capsule, which is surrounded by the barrier layer, osmogen layer and semi permeable membrane. A delivery orifice is made through these layers. When the system is in contact with the aqueous environment, water is imbibed & results in the development of hydrostatic pressure inside the system forcing the liquid formulation to break through the hydrated gelatine capsule shell at the delivery orifice.
Two types of L-OROS systems are available to provide controlled delivery of liquid drug formulations:
L-OROS hard cap,
L-OROS soft cap
Delayed liquid bolus delivery system

Colon Targeted Oral Osmotic System (OROS-CT): It is a system with 5-6 units of push pull enteric coated tablets filled in a hard gelatine capsule for targeted drug delivery to colon, after coming in contact with the GI fluids in the stomach the gelatine capsule dissolves but the enteric coating protects the units from the GI fluids, as they enter into the intestine, the enteric coating dissolves and water is imbibed into core, thereby causing the push compartment to swell and release the drug from the drug layer in a controlled manner.

Formulation of Osmotic Controlled Drug Delivery System:
Basic Components required for Osmotic Drug Delivery System are**:**

a) Drug: Drugs having biological half life between 1-6 hours and those which are used to treat chronic diseases are best candidate to prepare osmotic based formulations. In some cases drug itself may act as osmogen if it has good aqueous solubility, osmogenic salts and other sugars can be incorporated in the formulation if the drug is insoluble which does not act as osmogen.

b) Osmotic agent: The osmotic pump is driven by osmotic potential created by the presence of water soluble components within the tablet core. The most important consideration for selection of the osmogen is that it achieves sufficient osmotic pressure difference across the membrane to drive water into the tablet and that enough osmogen is present to sustain a saturated solution and intended delivery duration.

c) Pore forming agents: These agents are particularly used in the pumps developed for poorly water soluble drugs,
These pore forming agents form a micro porous membrane due its leaching property during operation.

- Alkaline metal salts such as sodium chloride, sodium bromide, potassium chloride, potassium sulphate, potassium sulphate, potassium phosphate etc.
- Alkaline earth metals such as calcium chloride, and calcium nitrate
- Carbohydrates such as sucrose, glucose, fructose, mannose, lactose, sorbitol, mannitol and diols, Polyols such as poly hydric alcohols and polyvinyl pyrrolidone.

d) Wicking Agent: A wicking agent is a material with the ability to draw water into the porous network of a delivery device. A wicking agent is either of swellable or non-swellable in nature. The function of wicking agent is to carry water to surfaces inside the core of the tablet, thereby creating channels or a network of increased surface area

e) Flux Regulating Agents: Delivery systems can be formulated to regulate the permeability of the fluid by incorporating flux-regulating agents in the layer. Hydrophilic substances improve the flux, whereas hydrophobic materials tend to decrease the flux.

- Flux enhancing agents: - hydrophilic substances such as polyethylene glycol (300-6000 Da), polyhydric alcohol, polyalkylene glycol.
- Flux reducing agents: - hydrophobic substances such as pthalates substituted with an alkyl or alkoxy, example: diethyl phthalate, dimethoxyethylphthalate.

f) Semi-permeable Membrane: An important part of the osmotic drug delivery system is the semi permeable membrane. Therefore, the polymeric membrane selection is important in the osmotic drug delivery formulation. The membrane should possess characteristics, such as

- Must be selectively permeable to water
- Should be biocompatible
- Rigid and non-swelling
- Should be sufficient thick to withstand the pressure within the device.

Polymers that are permeable to water can be used as a coating material in osmotic devices example: - cellulose acetate.

g) Coating Solvent: Solvents suitable for making polymeric solutions, 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 excipients in osmotic drug delivery. The mixtures of solvents such as acetone-methanol (80:20), acetone-ethanol (80:20), acetone-water (90:10), methylene chloride-methanol (79:21), methylene chloride-methanol-water (75:22:3) are commonly used.

Factors Influences the Release Rate in the Osmotic Controlled Drug Delivery Systems:

a) Osmotic pressure: Osmosis is the flow of water between two solutions separated by a semi permeable membrane caused by a difference in solute concentration, Osmotic pressure is the pressure which needs to be applied to a solution to prevent the inward flow of water across a semi permeable membrane, it is important to optimize the osmotic pressure gradient between the core and the external environment. 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.

Water influx through semi permeable membrane controls the delivery of drugs which can be described as:

$dv/dt = k.A(\sigma.\Delta\pi - \Delta P)$

where, dv/dt is the water influx

A is the membrane area

k is the permeability of the semi permeable membrane with respect to the solvent

σ is the osmotic reflection coefficient

ΔP and Δπ are the osmotic and hydrostatic pressure difference between the inside and outside of the system.

b) Solubility: Solubility of drug plays a major role in the drug release kinetics of osmotic controlled drug delivery systems. Therefore, drugs should have sufficient solubility to be delivered by osmotic delivery. Model drug for osmotic delivery should have solubility within the range of 50- 300 mg/ml. To improve the solubility of drug various solubility enhancement techniques are used. They are mentioned below

1. Use of wicking agents
2. Use of other salt form
3. Use of polymorph
4. Resin modulation approach
5. Use of swellable polymers
6. Use of effervescent mixtures

c) Size of Delivery Orifice: To get zero-order delivery profile, area of the orifice must be sufficiently large to minimize osmotic pressure build up in the system. Otherwise, the hydrostatic pressure can deform the membrane and affect the zero-order delivery rate. Therefore, the cross-sectional area of the orifice should be maintained optimum between the minimum and maximum values; orifice size is generally between 600 microns to 1 mm.

Methods to create a delivery orifice in the osmotic systems are:

1. Mechanical drilling: Done by manually drilling the orifice by special bench top equipment or by using needle to get the required diameter of the delivery orifice.
2. Laser drilling: This technology is well established for producing sub-millimetre size hole in tablets. Normally CO_2 laser beam is used for drilling purpose, which offers excellent reliability.
3. Indentation: In this type core tablets are made by using modified punches having needle on upper punch. The hole made by the indentation is not covered during coating process which acts as a path for drug release in osmotic system.
4. Use of pore forming substances in the semi permeable membrane coating: e.g. controlled porosity osmotic pump.

d) Use of Wicking Agent: Wicking agents help to increase the contact surface area and also increases the aqueous permeability of the drug. The use of the wicking agent in the formulation help to enhance the rate of drug released from the orifice of the drug. Examples are- Colloidal silicone dioxide, polyvinyl pyrollidine, sodium lauryl sulphate

e) Type and Amount of Plasticizer: Type and amount of plasticizer also influences the drug release from the osmotic controlled drug release

systems. In pharmaceutical industry coatings, plasticizers and 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 and 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 systems. Some examples of plasticizers are polyethylene glycols, ethylene glycol monoacetate, and tri ethyl citrate.

Advances in osmotic drug delivery:

Duros Technology: The DUROS pump conceptually resembles a miniature syringe in which drug is pushed out in highly controlled, minute dosages. Through osmosis, water from the body is slowly drawn through the semi-permeable membrane into the pump by salt (osmotic agent) residing in the engine compartment. The water drawn into the engine compartment expands the osmotic agent and slowly and continuously displaces a piston to dispense small amounts of drug formulation from the drug reservoir through the orifice. DURECT is holding an exclusive license from ALZA Corporation to develop and commercialize products in selected fields based on the DUROS® implant technology.

Telescopic capsule for delayed release: This device consists of two chambers first containing the drug and the exit port and second chamber containing the osmotic ingredients, a membrane made of wax like material separates the two sections, as fluid imbibed into the housing of the dispensing device the osmotic engine expand and exert pressure on the slidable first and second wall where they are joined and the drug is released into the external environment, in some cases according to the requirement the drug is loaded as delayed release pellets.

Table 1: Osmotic agents and their examples

Osmogens	**Example**
Inorganic water-soluble osmogens	Magnesium sulphate, Sodium chloride, Sodium sulphate, Potassium chloride, Sodium bicarbonate
Organic polymer osmogens	Sodiumcarboxy methyl cellulose, Hydroxypropylmethyl cellulose, methyl cellulose, Polyethylene oxide, Polyvinyl pyrrolidine
Carbohydrates	Arabinose, ribose, xylose, glucose, fructose, galactose, mannose, sucrose, maltose, lactose
Water-Soluble amino acids	Glycine, leucine, alanine, methionine

Table 2: 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	Chlorpheniramie Maleate	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	Implantable osmotic systems	-----
Viadur	Leuprolide acetate	Implantable osmotic systems	-----
Chronogesic	Sufentanil	Implantable osmotic systems	-----

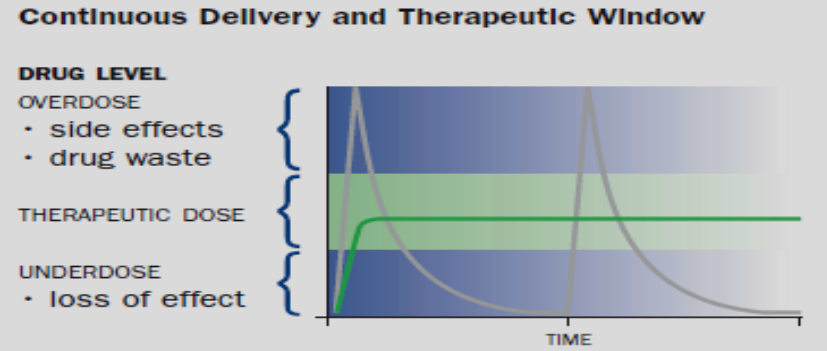

Figure 1: Plasma drug concentration of conventional —
Controlled release dosage form ▬

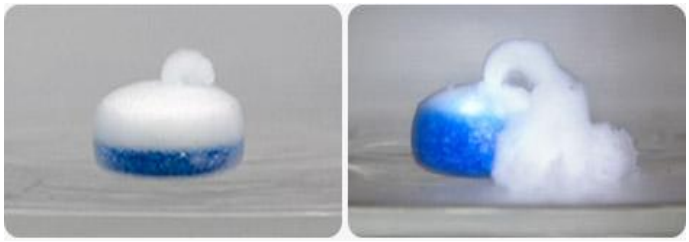

Figure 2: Zero order drug release from Osmotic pump

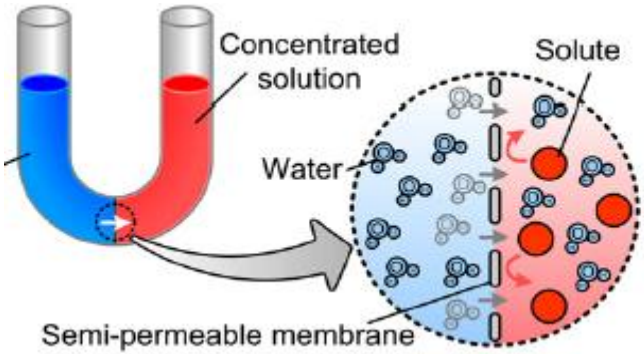

Figure 3: Principle of osmosis

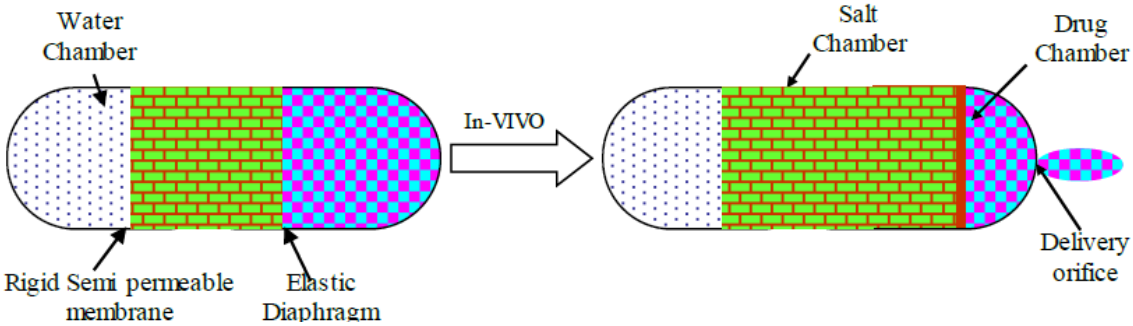

Figure 4: Rose-Nelson pump

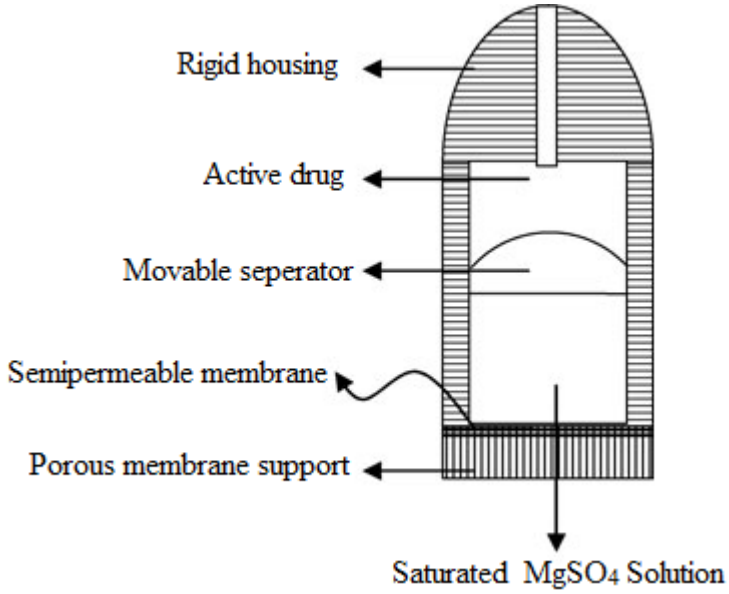

Figure 5: Higuchi Leeper osmotic pump

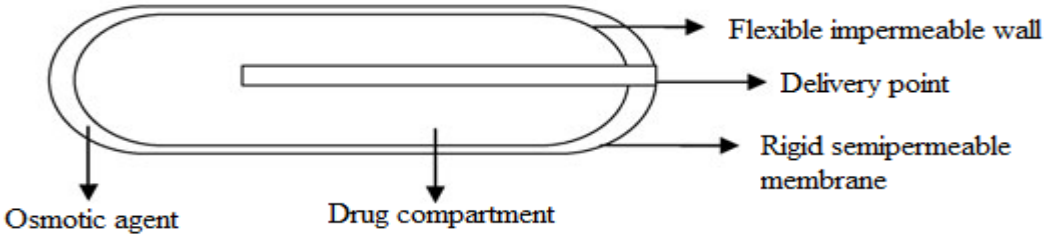

Figure 6: Higuchi- Theeuwes pump

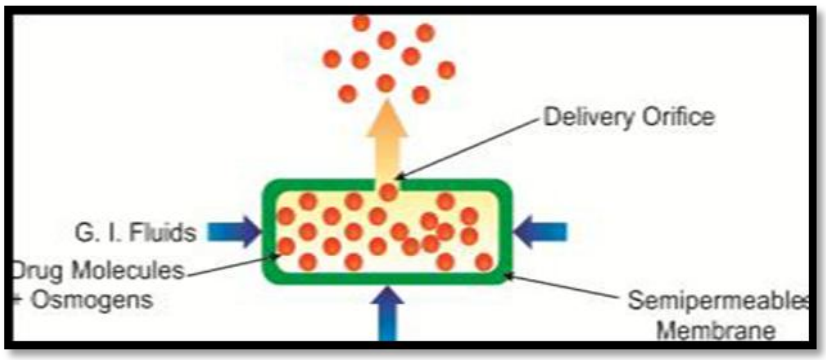

Figure 7: Elementary osmotic pump

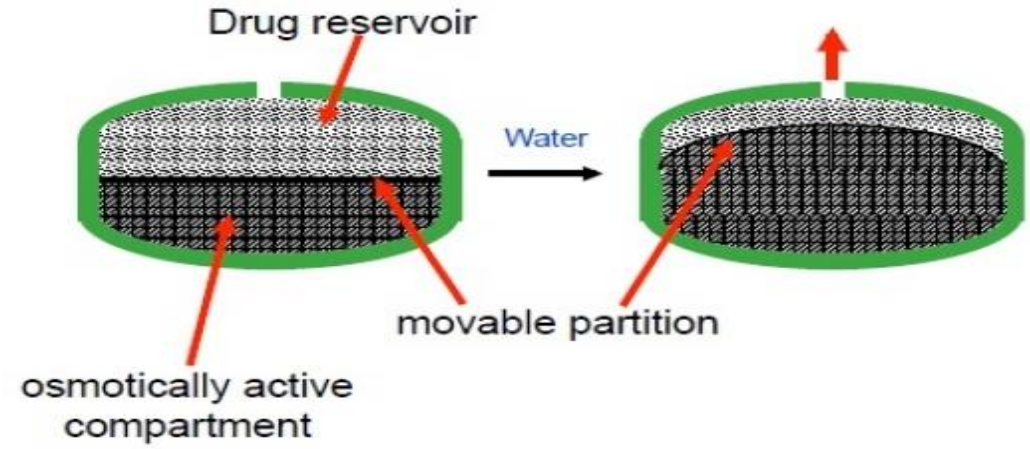

Figure 8: Push pull osmotic pump

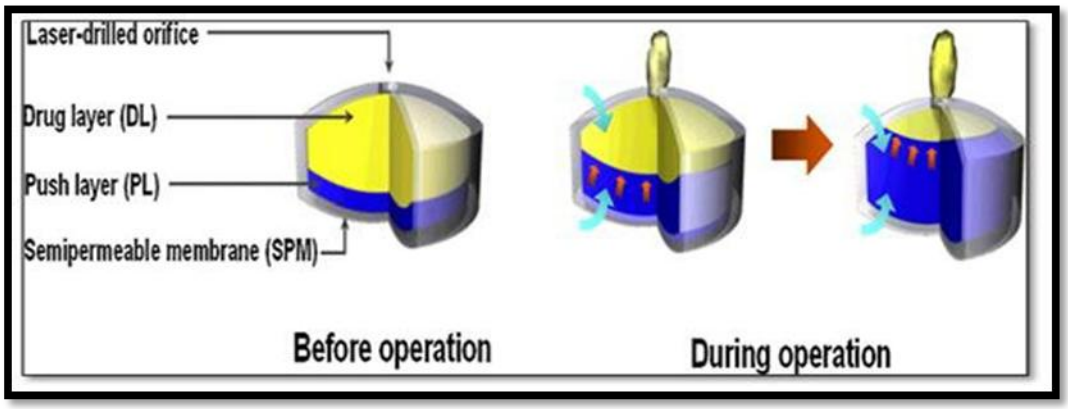

Figure 9: Mechanism of push-pull osmotic pump

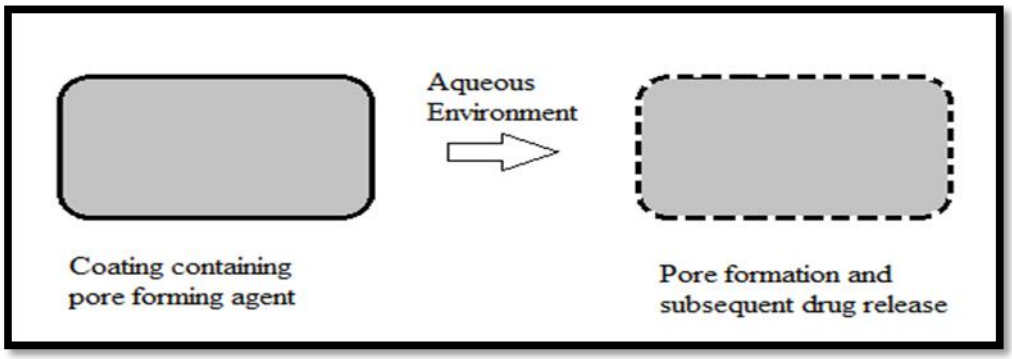

Figure 10: Controlled porosity osmotic pump

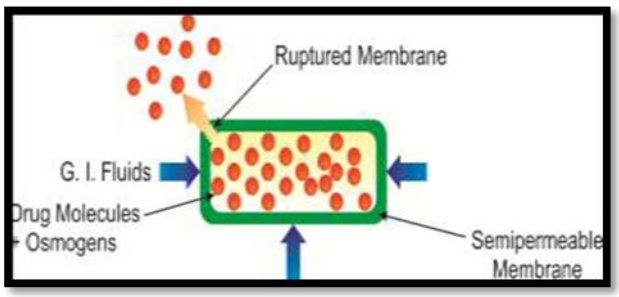

Figure 11: Bursting osmotic pump

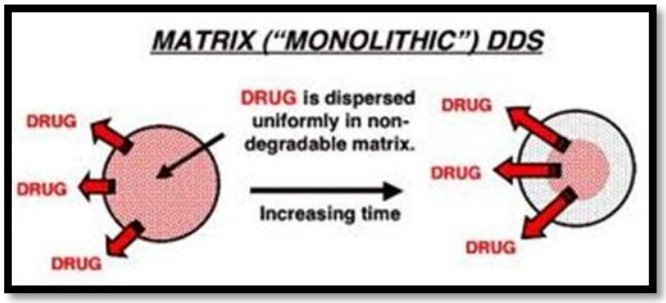

Figure 12: Monolithic osmotic system

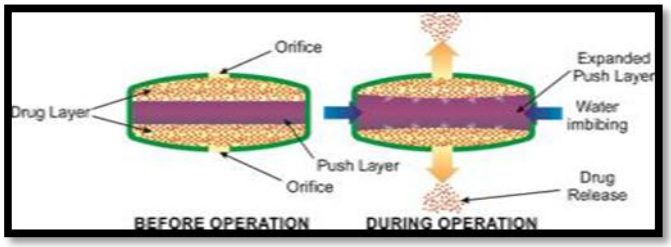

Figure 13: Sandwiched osmotic tablet

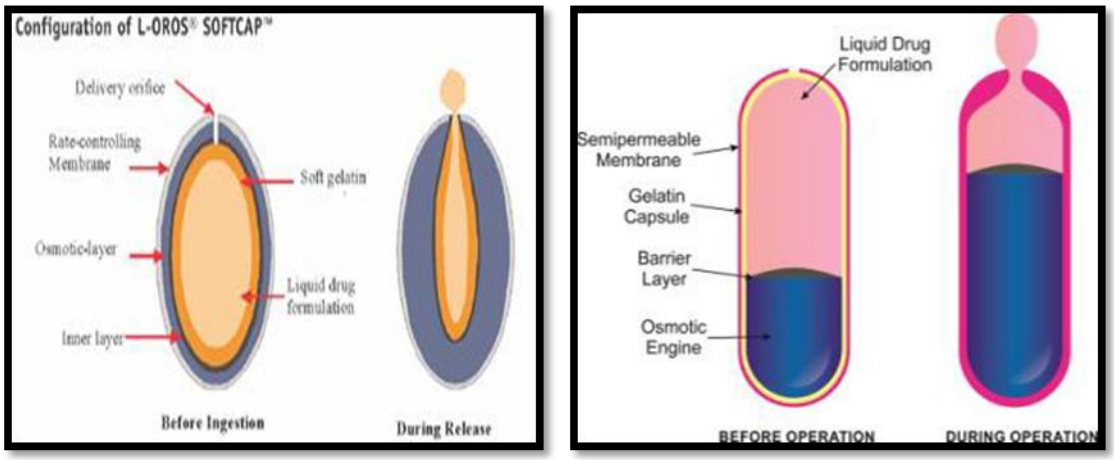

Figure 14: Liquid OROS

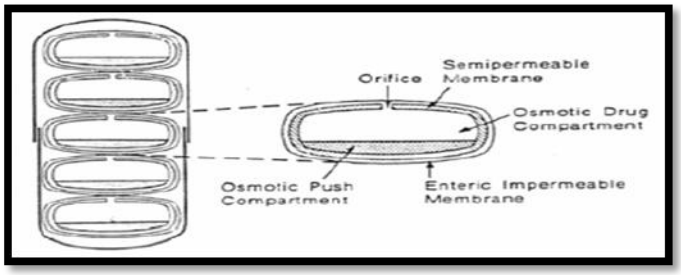

Figure 15: Colon targeted oral osmotic system

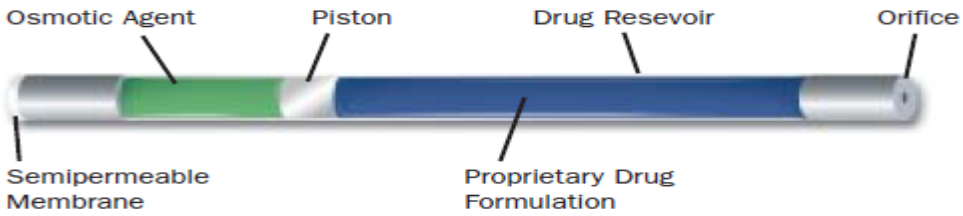

Figure 16: Duros technology

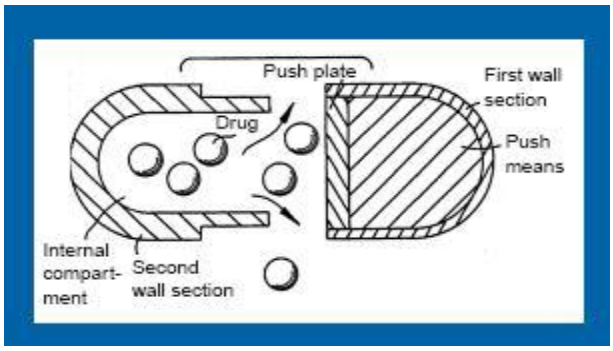

Figure 17: Telescopic capsule

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