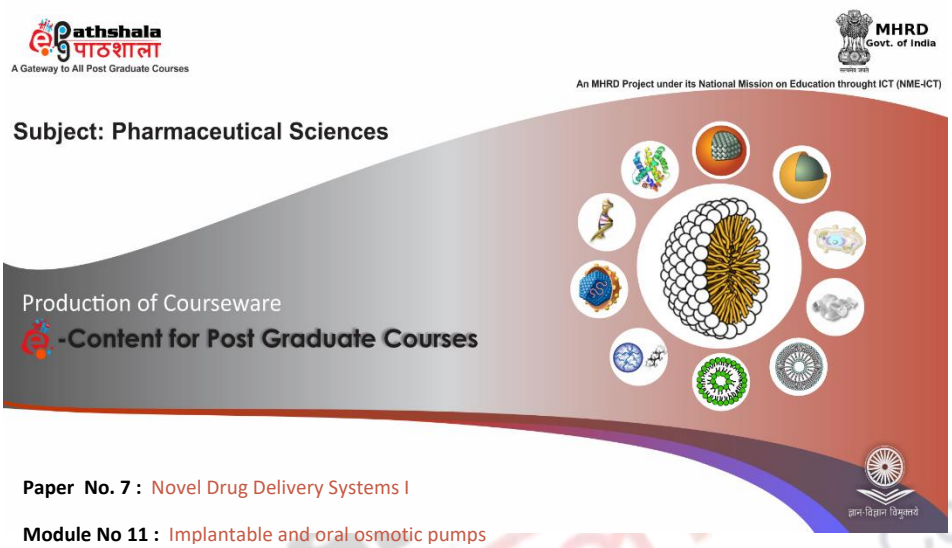

Paper No. 7 : Novel Drug Delivery Systems I

Module No 11 : Implantable and oral osmotic pumps

Development Team

Principal Investigator	Prof. Farhan J Ahmad Jamia Hamdard, New Delhi
Paper Coordinator	Dr. Zeenat Iqbal Jamia Hamdard, New Delhi
Content Writer	Dr. Sohail Akhter Jamia Hamdard, New Delhi
Content Reviewer	Prof Roop K Khar BS Anangpuria Institute of Pharmacy, Faridabad, Haryana, India

Description of Module	
Subject Name	Pharmaceutical Sciences
Paper Name	Novel Drug Delivery Systems I
Module Name/Title	Implantable and oral osmotic pumps
Module Id	
Pre-requisites	
Objectives	
Keywords	

Module 11: classification of OCDDS, implantables, oral osmotic pumps, specific types, disadvantages of OCDDS

CLASSIFICATION OF OSMOTICALLY CONTROLLED DRUG DELIVERY SYSTEM (OCDDS)

OCDDS is classified under these following categories:

1	**IMPLANTABLE**	• Rose-Nelson pump • Higuchi-Leeper pump • Higuchi-Theuwes pump • Implantable miniosmotic pump
2	**ORAL OSMOTIC PUMP**	• Single chamber osmotic pump ➢ Elementary osmotic pump • Multi chamber osmotic pump ➢ Push pull osmotic pump ➢ Osmotic pump with non-expanding second chamber
3	**SPECIFIC TYPES**	• Osmotic bursting osmotic pump • Controlled porosity osmotic pump • Liquid OROS • OROS-CT (colon targeting) • Sandwiched oral therapeutic system • Monolithic osmotic systems • OSMAT • Telescopic Capsule for Delayed Release

Preparation of osmotically controlled DDS

An osmotically controlled DDS comprises of the following main components:

- **Drug**: Highly potent drug with a short half-life is incorporated in the osmotically controlled drug delivery system.
- **Semi-permeable membrane**: The most common semipermeable membrane which is employed for osmotic pumps is made of cellulose acetate which is available in different acetyl content. Other polymers used includes agar acetate, amylase triacetate, betaglucan, poly(vinylmethyl)ether copolymers, poly(orthoessters)poly acetals and selectively permeable poly(glycolic acid) and poly (lactic acid) derivatives.
- **Polymers:** Many polymers can be used for formulating an osmotic delivery system. Water insoluble drugs can be entrapped in hydrophobic polymers such as such as ethyl cellulose and wax materials , moderately water soluble compounds can be entrapped in hydrophilic polymers such as hydroxy ethyl cellulose, carboxy methyl cellulose, hydroxyl propyl methyl cellulose, high molecular weight poly (vinyl pyrrolidone) whereas highly water soluble drugs are entrapped in non-swellable polymers.

- **Wicking agents**: These are the swellable or non-swellable agents which have the ability to draw water to the porous bed of delivery device. They have the following characteristic:
  a. They undergo a process of physiosorption which is a phenomenon in which Vander waals interactions between the surface of the wicking agent and the absorbed molecule result in a loose attachment of the solvent molecules to surface of the wicking agent via.
  b. Wicking agents carry water to the surface inside the osmotic device leading to formation of numerous pores, thereby increasing its surface area.

  Examples of wicking agents include kaolin, bentonite, colloidal silicon dioxide, sodium lauryl sulphate (SLS), titanium dioxide etc.

- **Osmogens**: These are the agents which are used to achieve optimum level of osmotic pressure inside the system. They include carbohydrates and inorganic salts.
- **Solubilising agents**: Solubilizing agents can be of three types: 1) Those which inhibit the crystal formation of the incorporated drugs, e.g. PVP, alpha and beta- cyclodextrins etc. 2) A high HLB micelle- forming surfactant, e.g. tweens or spans, citrate esters and their combinations with anionic surfactants. eg alkyl esters particularly tri ethyl citrate.
- **Surfactants**: These are the agents which improve the blending of the various components of the system. Examples include Polyoxy ethylenated castor oil having ethylene oxide, glyceryl laureates, Poly oxy ethylenated glyceryl lecinoleate etc.
- **Coating solvents**: These are the organic or inorganic agents which are used for manufacturing the wall of the osmotic device. Examples of such agents include methanol, ethanol, acetone, isopropyl alcohol, methylene chloride etc.

- **Reforming agents**: These are the agents who are used in the pumps which are developed for poorly water soluble drug and also in the development of multiparticulate osmotic pumps. These are usually pore forming agents which cause the formation of microporous membrane. Examples of reforming agents include alkaline metal salts such as sodium chloride, sodium bromide, potassium chloride and potassium phosphate. Typical examples of pore forming agents include alkaline earth metals such as calcium chloride and calcium nitrate, carbohydrates such as sucrose, glucose, fructose, maltose, lactose, sorbital, mannitol and polyols such as polyhydric alcohols and polyvinylpyrrolidone.
- **Plasticizers**: These work to lower the second order phase transition temperature of the wall thereby increasing the flexibility and also the fluid permeability. Approximately 0.001 to 50 parts of a plasticizer or a mixture of plasticizers are added to 100 parts of wall forming materials. E.g. dialkyl phthalates and other phthalates, tristyl phosphates and other phosphates, alkyl adipates , triethyl citrate and other citrates, acetates, propionate, glycolates, glycerolates, myristates, benzoates etc.
- **Flux regulators:** Flux regulators are used from 0.001 parts to 50 parts and are added to the wall forming material to regulate the fluid permeability. They also enhance the flexibility and porosity of the lamina. Examples of flux regulator include poly hydric alcohols such as poly alkylene glycols and low molecular weight glycols such as poly propylene, poly butylenes and poly amylene etc.
- **Pore forming agents:** Pore forming agents are used in case of pumps delivering water insoluble drugs or in development for multiparticulate osmotic pumps. These agents results in the formation of pores which forms a microporous membrane. Reforming agents include
  1) Alkaline metal salts like sodium chloride, sodium bromide, potassium chloride and potassium phosphate,
  2) Alkaline earth metals like calcium chloride and calcium nitrate,
  3) Carbohydrates like sucrose, glucose, fructose, maltose, lactose, sorbital, mannitol and
  4) Polyols such as polyhydric alcohols and polyvinyl pyrrolidone.

1. Implantable osmotic drug delivery system

A. Rose-Nelson pump

The Rose-Nelson pump is one of the earliest discovered osmotic devices. It is comprised of a water chamber, a salt chamber and a drug reservoir. A rigid semipermeable membrane is present between water chamber and salt chamber, while the salt and drug chamber is separated by an elastic diaphragm.

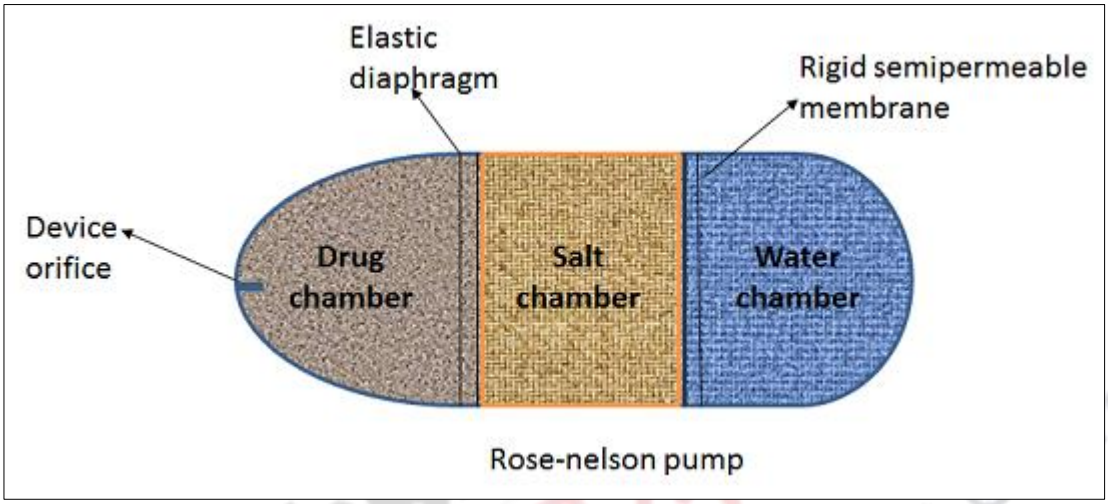

Figure1: Schematic diagram of Rose-Nelson pump

Due to the development of osmotic pressure gradient across the semipermeable membrane, water enters inside the salt chamber (from lower concentration to the higher concentration of solute). This increases the volume of salt chamber. At the same time elastic diaphragm distends to push the drug out of the device. The design and mechanism of this pump resembles the push-pull osmotic pump. The major limitation of this pump is the water chamber that needs charging before it can be used.

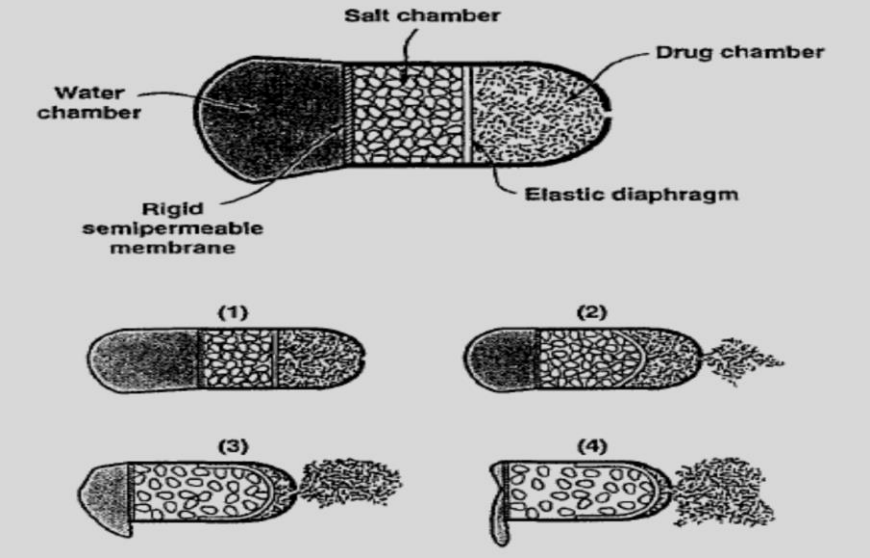

Figure2: Mechanism of drug release from the Rose-Nelson pump

B. Higuchi-Leeper pump

This device is different from the Rose-Nelson pump, as it does not contain an inbuilt water chamber. It consists of a rigid housing and has a porous support for the semipermeable membrane at the back, from where water enters into the device. The salt chamber contains saturated salt solution. Higuchi-Leeper pump works on the principle of imbibition of water from the surrounding. When the device is swallowed or implanted in the body, the activation of the pump takes place which results in the penetration of the surrounding biological fluid into the device through the porous semipermeable membrane. This inflow of fluid dissolves the salt resulting in the creation of osmotic pressure which pushes the movable separator toward the drug chamber to exclude the drug outside the device. This type of pump is widely used for veterinary purpose for the delivery of antibiotics or growth hormones to animals. Due to absence of inbuilt water chamber, this device is less susceptible to microbial contamination. Hence, it can be stored for longer duration of time before use.

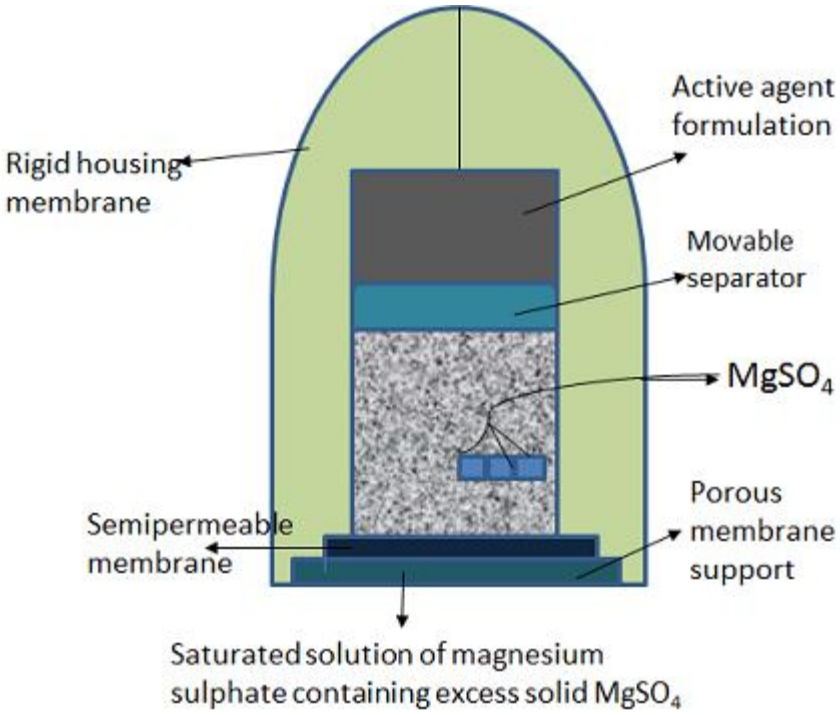

Figure3: Schematic diagram of Higuchi-Leeper pump

C. Higuchi-Theeuwes pump

This device has a similarity with Higuchi-Leeper pump as it is also devoid of water chamber. It is a further simplified variant of Rose-Nelson pump developed by Higuchi and Theeuwes. Unlike the Higuchi-Leeper pump, Higuchi-Theeuwes pump contains a semipermeable membrane attached to the outer rigid housing of device. There is a layer of solid osmogen, dispersed in a suitable solvent beneath the outermost layer. The innermost layer of device consists of flexible and collapsible material. The drug reservoir is present inside the device and it is directly connected with the delivery orifice.

When this osmotic pump comes in contact of body fluid, water enters inside the pump through semipermeable membrane thereby exerts pressure on the innermost, flexible wall to pump the drug out.

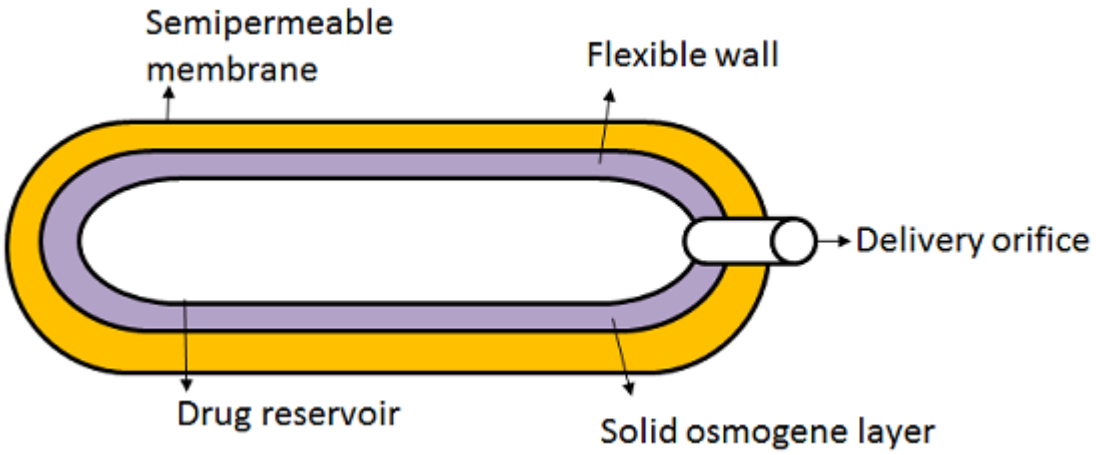

Figure4: Schematic diagram of Higuchi-Theeuwesh pump

D. Implantable miniosmotic pump

This pump is similar to Higuchi-Theeuwes pump, except it has an additional component, flow moderator which is inserted inside when the device is already filled with the drug solution or suspension.

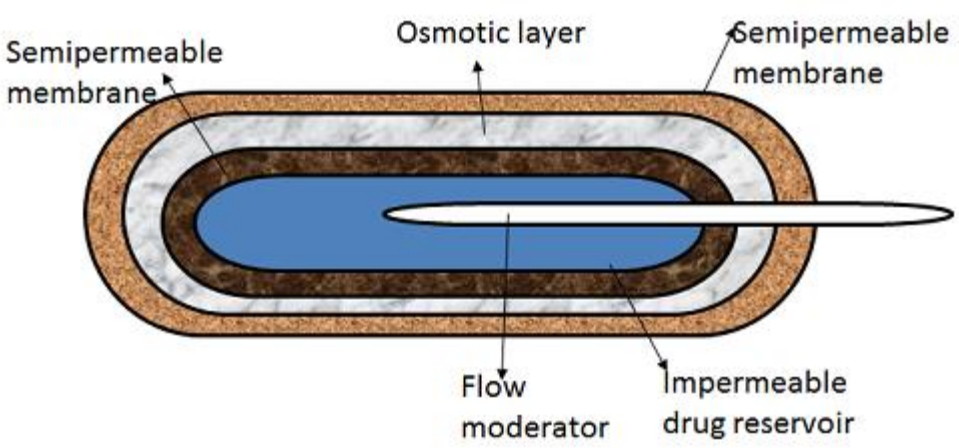

Figure5: Schematic diagram of Implantable miniosmotic pump

Table1: Scale of main types of implantable osmotic pumps

IMPLANTABLE OSMOTIC PUMPS	APPROXIMATE VOLUME (cm^3)	COMPONENTS
		1. Rigid housing

Rose-Nelson pump	**80**	**2. Water chamber** **3. Salt chamber** **4. Drug chamber** **5. Elastic diaphragm** **6. membrane**
Higuchi-Leeper pump	**35**	**1. Rigid housing** **2. Salt chamber** **3. Drug chamber** **4. Elastic diaphragm** **5. membrane**
Higuchi-Theuwes pump	**3**	**1. Salt chamber** **2. Drug chamber** **3. Elastic diaphragm** **4. membrane**
Implantable miniosmotic pump	**<1**	**1. Drug chamber** **2. membrane**

1. OSMOTIC PUMPS FOR ORAL DELIVERY

1.1. Single Chamber

Drug release from single compartment osmotic pumps initially follows zero order release kinetic and is favored by saturated solution of drug. The moment at which drug solution gets diluted, drug release follows first order kinetic.

Elementary Osmotic pump

Felix Theeuwes first designed and published the concept of elementary osmotic pump (EOP) in 1975. EOP consists of active ingredients having desirable osmotic pressure shaped in the form of a tablet and coated with a semi permeable membrane, generally made of cellulose acetate. A small orifice is pierced through the semi permeable membrane to facilitate the release of drug. When this tablet is

placed in the aqueous environment, water gets inside through semi permeable coating due to osmotic pull and a saturated drug solution is formed. Since the coating membrane is non-extensible, further rise in volume due to more uptake of water creates hydrostatic pressure inside the tablet core and the drug is released at a controlled rate from the delivery orifice in the membrane. However, generally a lag time of 30-60min have been observed before the drug is released owing to the hydration of the system, after which the drug is delivered with almost zero order release kinetics up to around 70 percent of the total drug content. Control of rate of the drug release depends on the water permeation properties of the semipermeable membrane around the formulated agent, and osmotic properties of the formulation. EOP systems are appropriate for the delivery of drugs having moderate to high aqueous solubility.

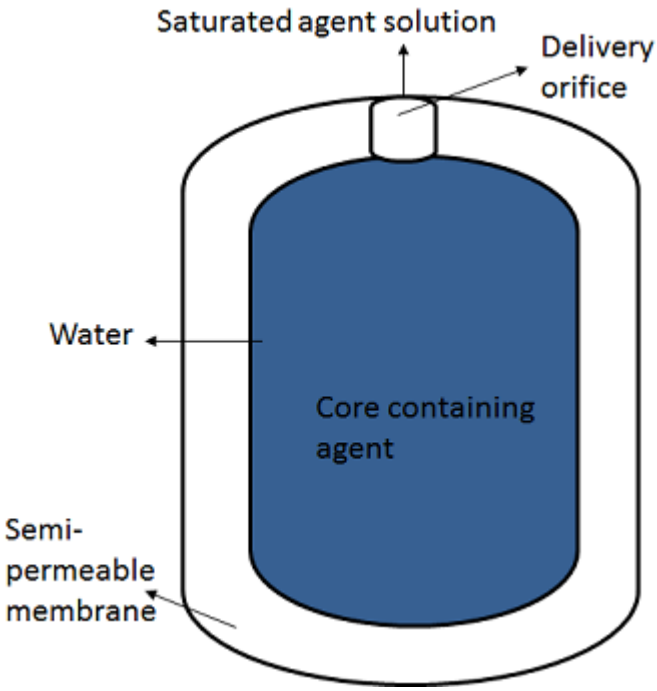

Figure6: Elementary osmotic pump

B. Multi chamber osmotic pump

Drug release from multi compartments usually follows zero order kinetic throughout the operation.

i) Push-pull osmotic pump

Push pull osmotic pump is a modified form of EOP and has been used for the delivery of both hydrophilic and hydrophobic drugs. Structurally, it consist of a bilayer core namely 'drug layer' and 'push layer', enclosed within a semipermeable membrane having a laser-drilled orifice. But here, the core of compressed tablet is further divided into two compartments. One compartment (depicted as upper layer in the figure7 consists of osmotic core drug (60-80%) and the other compartment possesses polymeric osmogen (20-40%). The core component of this pump is compressed to form a tablet and then coated by a semipermeable membrane. Mechanical or laser drill is used to create a hole in the semipermeable membrane. As compared to the earlier single-core EOP design, the polymeric drug layer of the bilayer core allows the drug to be solubilized or dispersed while polymeric push layer swells and generates enough pressure to allow the drug release under zero-order kinetics. Studies revealed that irrespective of the solubility of the drug, four key determinants i.e. Plasticizer in the membrane, surface area of the system, content of the osmotic agents and the drug layer polymer grade were governing the drug release in these systems.

The word "pull" and "push" is used in combination here to assign the name of this pump. The "pull" word signifies the imbibition of gastro-intestinal fluid by the osmotic core drug and polymeric osmogen. Whereas, the word "push" is used for, the pressure exerted by swollen polymer to expel the fine dispersion of drug, out of the device.

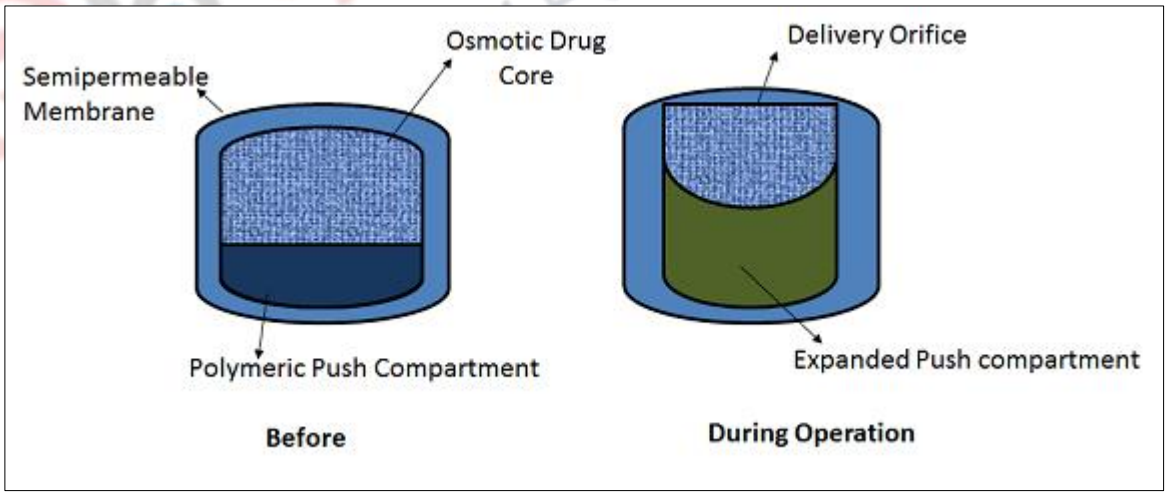

Figure7: Schematic diagram of a push–pull osmotic pump

ii) Osmotic pump with non-expanding second chamber

This device is also an example of multi chamber osmotic pump, but it is different from the push-pull osmotic pump, as it does not contain an expandable second chamber. These devices with non-expandable second chamber are further categorized into two subcategories, based on the role of their second chamber.

In first subcategory, second compartment acts as a diluting chamber for the drug solution coming out from the device. This function is particularly helpful in situations, where saturated solution of drug may cause gastro-intestinal irritation. For example; Osmosin®, a brand name of sodium indomethacin trihydrate was withdrawn from the market due to this gastro-intestinal irritation, caused by the concentrated solution of indomethacin salt. Structurally, this device is made up of two compartments. First compartment contains the drug and the second compartment possesses water soluble diluents, such as glucose, mannitol, sodium chloride etc. Both the compartment is compressed to form a bilayer tablet and this tablet is further coated by semipermeable membrane. The delivery orifice is created either by laser or by manual drilling. Water molecules enter the osmotic pump through the semipermeable membrane in response to the concentration gradient created across the device. This movement of water molecules inside the pump leads to the formation of concentrated solution of drug. This concentrated solution in turn moves to the second chamber to get diluted and finally comes out through the delivery orifice.

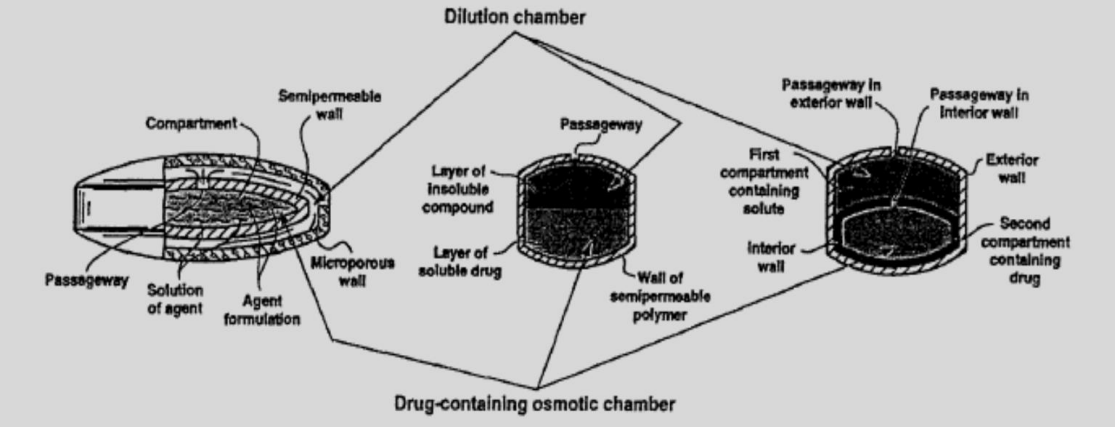

Figure8: Osmotic pumps with a drug-dilution chamber

The other subcategory of osmotic pump with non-expanding second chamber is shown in figure9.

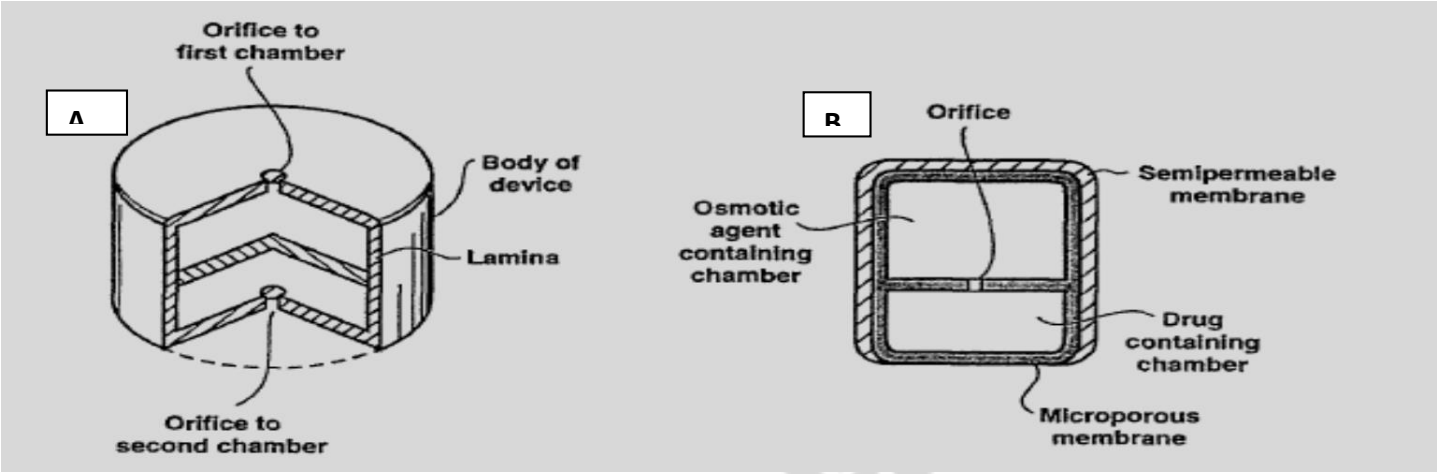

Figure9: Example of multichamber osmotic devices with chambers separated by rigid non-expanding wall

Here both the chambers of osmotic pump are separated by a rigid and impermeable wall and exploited for the controlled delivery of two different drugs simultaneously (Figure 9A).

The other variant of this above mentioned pump is made up of two rigid chambers (Figure 9A). The first and second chamber possesses osmogen and drug respectively. Both the chambers are connected by a central hole. The whole device is surrounded uniformly by a semipermeable membrane, except the front part of second chamber, where it remains in the form of microporous membrane.