A COMPREHENSIVE REVIEW ON OSMOTICALLY CONTROLLED ORAL DRUG DELIVERY SYSTEM

[1]Dhole Akshay V*, [2] Savita Deokar, [3]Dr. Sonia Singh

[1]M Pharmacy, Department of Pharmaceutics, Alard College of Pharmacy, Pune, India.

[2]Assistant Professor, Department of Pharmaceutics, Alard College of Pharmacy, Pune, India.

[3]Principal, Alard College of Pharmacy, Pune, India.

ABSTRACT:- Oral route is one of the most extensively used routes for drug administration for several advantages. In conventional oral drug delivery system, the release rate of drug cannot be controlled and effective concentration at the target site achieved is low. Bioavailability of drugs from the oral drug delivery may vary significantly, depending on factors such as physicochemical properties of the drug, presence of excipients, various physiological factors such as the presence or absence of food, pH of GIT, GI motility. OROS is an advanced drug delivery system that uses osmotic pressure as a driving force to deliver drug in a controlled manner for a longer period of time. In this review article, historical aspects related to osmotic pump, various types of osmotically controlled pumps like EOP, PPOS, CPOP, etc have been studied. The basic components which are required for developing an oral osmotically controlled release formulations and factors affecting on release characteristics drug from an osmotic system have been discussed briefly.

KEYWORDS:- Bioavailability, OROS, EOP, PPOP, CPOP, etc.

I. INTRODUCTION

Oral drug delivery system is the most acceptable and most extensively used route of administration because it provides maximum active surface area for absorption of drug and local as well as systemic effect can be achieved by this route of administration. Many conventional drug delivery system have been designed by the various researchers to modulate the release characteristics of drug over an extended period of time. In traditional/conventional drug delivery system, rate & extent of drug absorption depends on various factors such as physiochemical properties of drug, physiological condition of body like presence or absence of food in GI tract, GI motility, pH of GI tract & so on. There is no control over the drug release from traditional drug delivery system and efficient concentration of drug at the target site is low or minimal. To overcome these limitations many designs are available to control or modulate the drug release from dosage forms. Majority of oral controlled release dosage forms falls in the category of matrix, reservoir and osmotic system. Generally the release of drug from matrix and reservoir, shows bioavailability problems due to gastric pH variation. Apart from that, osmotically controlled oral drug delivery system (OCDDS) is one of the most promising drug delivery technology that uses osmotic pressure as a driving force to controlled the release of medicament over an extended period of time which improves therapeutic effect and minimizes unintended side effects. Drug release from OCDDS is independent on biological pH, hydrodynamic conditions of the body and

other physiological parameters to a large extent. and it is possible to modulate release characteristics by optimizing the properties of drug and system.[1][2][3]

II. ADVANTAGES

- Drug discharge from the osmotic pump is free of the hydrodynamic conditions of the body and gastrointestinal pH of biological media.
- Drug release from osmotic system follows zero order kinetics.
- Compared to traditional diffusion controlled DDS, high amount of drug release from Osmotic System.
- Drug release from osmotic systems is highly predictable and can be programmed by modulating release controlling parameter of semipermeable member which was done by using different polymer.
- Release of drug from osmotic system is minimally affected by presence of food in GI tract.
- A high degree of in-vitro-in-vivo Correlations (IVIVC) is obtained from osmotic system.
- Osmotic system delivery the drug, delayed or pulsed, if needed.
- Drug release form the osmotic system in a controlled manner, which improve the therapeutic effects as well as improve patient compliance by reducing dosing frequency.
- Increase margin of safety of highly potent drug.[1][2][4]

III. DISADVANTAGES

- Retrieval therapy is not possible in case of unexpected adverse event.
- High cost because it required special instruments such as laser drilling machine.
- Rapid development of tolerance.
- It may causes irritation or ulcer due to release of saturated solution of drug.
- Dose dumping, if coating is improper.
- Drug release from osmotic system is highly dependent on membrane thickness and size of drilled hole.[2][5]

IV. PRINCIPLE & BASIC CONCEPT OF OSMOTIC DRUG DELIVERY SYSTEM

Osmolarity: - Osmolarity is the number of osmoles per litre of solution.

Osmolality: - Osmolarity is the number of osmoles per Kg of water.

Osmosis: - Osmosis can be defined as movement of solvents from lower concentrations to higher concentration through a selectively permeable membrane until equilibrium is achieved.

Osmotic Pressure: - Osmotic pressure is a colligative property of a solution in which the scale of osmotic pressure of the solution is self-governing on the number of separate entities of solute present in the solution. Osmotic pressure created inside the core of device due to imbibition of fluid from external atmosphere into the dosage form & regulates the delivery of drug from osmotic device. Speed of drug release from osmotic pump is directly proportional to the osmotic pressure.[6]

Principle Of Osmosis

The first information of an Osmotic effect was observed by Abbenollet (1748)**.** But**,** in 1877, Pfeffer performed an experiment using semi-permeable membrane to separate sugar solution from pure water. He demonstrated that the osmotic pressure of the sugar solution is directly proportional to concentration solution and the absolute temperature. In 1886, Vant Hoff acknowledged the underlying proportionality between osmotic pressure, concentration and

temperature. He acknowledges that osmotic pressure is proportional to concentration and temperature and the relationship can be described by following equation.[6][7]

$$\Pi = p\ c\ RT \quad \text{..... (1)}$$

Where,

Π = osmotic coefficient of the solution

p = Osmotic pressure of concentration of solution

c = molar concentration of sugar in the solution

R = gas constant and

T = Absolute temperature

V. HISTORICAL ASPECTS RELATED TO OSMOTIC PUMP[1][5][8]

Table 1: historical aspect related to osmotic system

Year	Comments	Reference
1748	First report of osmosis	Banker, 1987
1877	Quantitative measurement of osmotic pressure	A Martin, 1993
1955	First osmotic pump by Rose and Nelson	Rose et al, 1955
1973	Higuchi-leeper introduced a new version of Rose and Nelson pump with certain modifications	Santus et al, 1995
1973	Osmotically powdered agent dispense device with filling means	Theeuwes, 1984
1975	Major milestone in the field of osmotic drug delivery introduced the first oral osmotic pump i.e. E.O.P	Cortese et al, 1982
1976	Patent granted on the design of Alzet osmotic pumps which later extensively used as an experimental tool in laboratory animals.	Theeuwes et al, 1984
1979	Osmotic bursting drug delivery device.	Chien et al, 1984
1982	Patent issue for an osmotic system which consist of a layer of a fluid swellable hydro gel to deliver insoluble to very insoluble drug.	Cortese et al, 1984
1984	First report of combination therapy by use of push-pull osmotic pump	Theeuwes et al, 1984
1985	Controlled porous osmotic pump was developed	Zentner et al, 1991
1986	Patent issue claiming a delivery for controlled administration of drug to ruminants	Mishra et al, 2006
1989	Developed push-pull osmotic pump for Nifedipine (Procardia XL) by Pfizer which was the largest selling cardiovascular product in US market until 1995.	Mishra et al, 2006 and Wilson et al,2000
1995	Patent to an osmotic dosage form for liquid drug delivery	Mishra et al, 2006
1999	Asymmetric membrane capsule was introduced	Mishra et al, 2006
2000	DUROS Leurpolid implants i.e. Viadur approved as first implantable osmotic pump for humans by US FDA	Mishra et al, 2006
2001	Patent granted for dosage form comprising liquid drug formulation that can self-emulsify to enhance the solubility, dissolution and bioavailability of drug	Mishra et al, 2006
2003	First report osmotic floating system	Mishra et al, 2006

VI. CLASSIFICATION OF OSMOTICALLY CONTROLLED DRUG DELIVERY SYSTEM[4][9][10]

A. Implantable osmotic pump

1. The Rose and Nelson pump
2. Higuchi Leeper pump
3. Higuchi Theuwes pump
4. Implantable mini-osmotic pump

B. Oral osmotic pump

1. **Single chamber osmotic pump**
   1) Elementary osmotic pump
2. **Multi chamber osmotic pump**
   1) Push pull osmotic pump
   2) Sandwiched osmotic pump
   3) Osmotic pump with non-expanding second chamber
3. **Specific types**
   1) Controlled porosity osmotic pump
   2) Osmotic bursting osmotic pump
   3) Liquid OROS
   4) Monolithic osmotic pump tablet
   5) Colon targeted oral osmotic system
   6) Asymmetrical membrane osmotic tablet
   7) Telescopic capsule for delayed release
   8) Multi particulate delayed release system (osmotic pellets)
   9) Effervescent osmotic pump tablet
   10) Self- emulsified osmotic tablet

A. Implantable Osmotic Pump

1. **The Rose & Nelson Pump**

In 1955 the two Australian scientists, Rose and Nelson reported first osmotic pump. Osmotic pump consist of three chambers i:e are,

- A drug chamber with orifice
- A salt chamber contains excess solid salt
- A water chamber

The drug and water chambers are separated from each other by a rigid semi-permeable membrane. The difference in osmotic pressure across the membrane, as a result water moves from water chamber into salt chamber. The volume of salt chamber increases because water enters into that chamber, which distends the latex diaphragm separating the salt and drug chambers, thereby pumping drug out of the device. The major disadvantage associated with this pump is, the water chamber must be charged before the use of this pump. Several modifications is done by Alza corporation in the Rose and Nelson pump. The pumping rate of Rose-Nelson pump is given by the following equation.[8][11]

$$dm/dt = dv/dt * C \quad \text{..... (2)}$$

Where,

dm/dt= drug release rate,

dv/dt= volume of water flow into salt chamber,

C= Concentration of drug into the drug chamber.

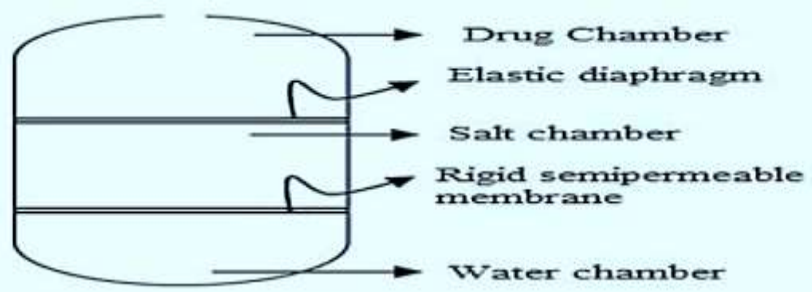

figure 1: the rose & nelson pump

2. Higuchi Leeper Pump

The Higuchi Leeper pump is a simply modified version of Rose-Nelson pump which is done by Alza Corporation in the early 1970s. The Higuchi Leeper pump is differ from Rose-Nelson pump is that there is no water chamber in that and the device is activated by water comes from the surrounding environments. Higuchi Leeper pump is mostly used for veterinary purpose. This type of pump is either swallowed or implanted in the body of animals for delivery of antibiotic or growth hormones. Higuchi Leeper pump comprises a rigid housing chamber, a semipermeable membrane is supported on a perforated frame and a salt chamber containing a fluid solution with an excess amount of solid salt. Upon administration/implantable of this pump, surroundings biological fluids enters into the device and dissolve MgSo4, creating osmotic pressure inside the device that pushes the movable separator towards the drug chamber as a result drug is remove outside the device. Recent modification in Higuchi Leeper pump accommodated pulsatile drug delivery system. Pulsatile release was achieved by the production of a critical pressure at which delivery orifice opens and release the drug.[8][12][13]

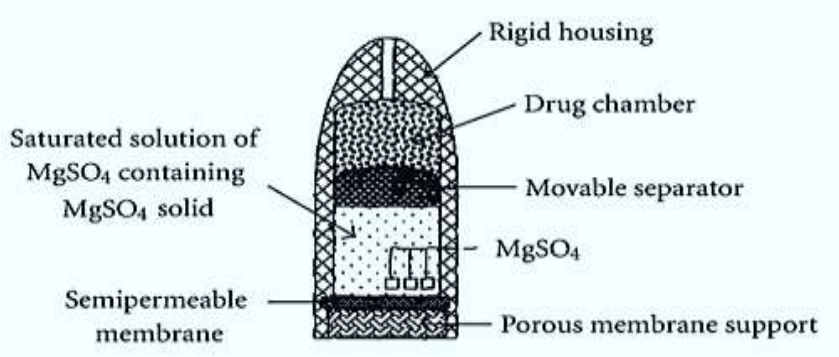

figure 2: higuchi leeper pump

3. Higuchi-Theeuwes Pump

This pump is also modified version of Rose-Nelson pump. In this device the rigid housing part is made up of semi-permeable membrane which is enough strong to with stand with the pumping pressure developed inside the core of the device due to permeation of water. The release of drug from device can be controlled by salt used in chamber, the permeability characteristic of outer membrane and orifice.[8][9]

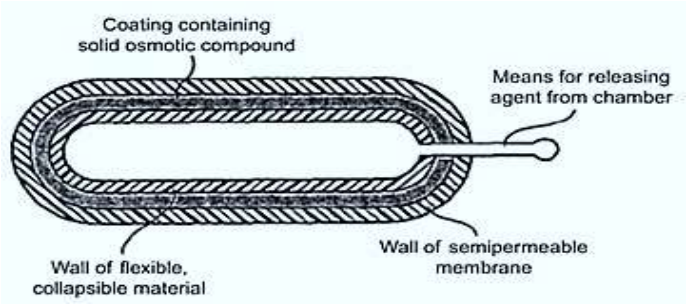

figure 3: higuchi-theeuwes pump

4. Implantable Mini Osmotic Pump

Implantable mini osmotic pump consists of three separate layers i:e the drug reservoir, the osmotic layer and a semi-permeable membrane that regulate the drug release rate. The extra compartment is present called flow moderator is inserted into the body of the osmotic device. An osmotic sleeve, a cylinder with a high concentration of osmotic agent, is the innermost chamber of the drug reservoir.The osmotic sleeve is protected by a rate-controlling semi-permeable membrane. When the system is placed in aqueous environment water enters into the osmotic sleeve through rate-controlling semi permeable membrane, compresses the flexible drug reservoir as a result, saturated drug solution is delivered by flow moderator. These pumps are accessible with variety of delivery rates between 0.25 to 10ml per hour and delivery duration between one day and four weeks. Example: Alzet osmotic pump.[(4)(9)]

B. Oral Osmotic Pump

1. Single Chamber Osmotic Pump

1) Elementary Osmotic Pump

In the 1974 Theeuwes invented an elementary osmotic pump (EOP). Elementary osmotic pump is a simplest osmotic pump which delivery the drug in a controlled manner for longer period of time, which depends upon water permeation characteristic of rate-controlling semi-permeable membrane and osmotic properties of formulation. Basically the system consists of three chamber i:e an osmotic core (containing drug with or without osmotic agent) enclosed by the rate controlling semi-permeable membrane having one laser drilled orifice on it (size varies from 0.5-1.5mm), which is done either by mechanical or by using laser drilled machine. When this osmotic device is in contact with aqueous environment, water is enters into system through semipermeable membrane and dissolving drug and osmotic agent (which create osmotic pressure inside the core), as a saturated solution of drug is delivered through the orifice in a controlled manner. The main disadvantage of elementary osmotic pump is that, it is only suitable to deliver water soluble drug.[(2)(4)(14)]

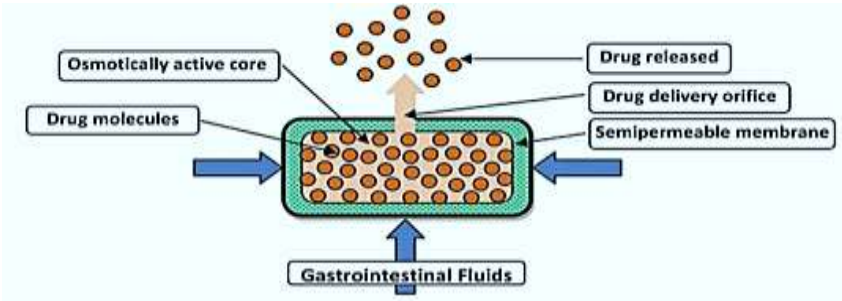

figure 4:elementary osmotic pump

2. Multi Chamber Osmotic Pump

1) Push Pull Osmotic Pump(PPOP)

PPOP is a modified version of elementary osmotic pump which appeared in 1980s, through which it is possible to deliver both poorly water soluble as well as highly water soluble drugs in a controlled manner. PPOP consists of two layers, in which one layer contains drug with or without osmotic agent and other layers contains osmotic agent with expandable polymeric agents. A rate-controlling semi-permeable control the water influx into both layers. When this osmotic device comes in contact with aqueous environment water is penetrate through the semi-permeable membrane and dissolve osmotic agent (which create osmotic pressure inside the core) and expandable polymeric agents expand it as results saturated solution drug is delivered through the laser drilled orifice at a constant rate. Major limitation of this system is difficult to delivery a orifice up to the drug compartment.(4)(10)

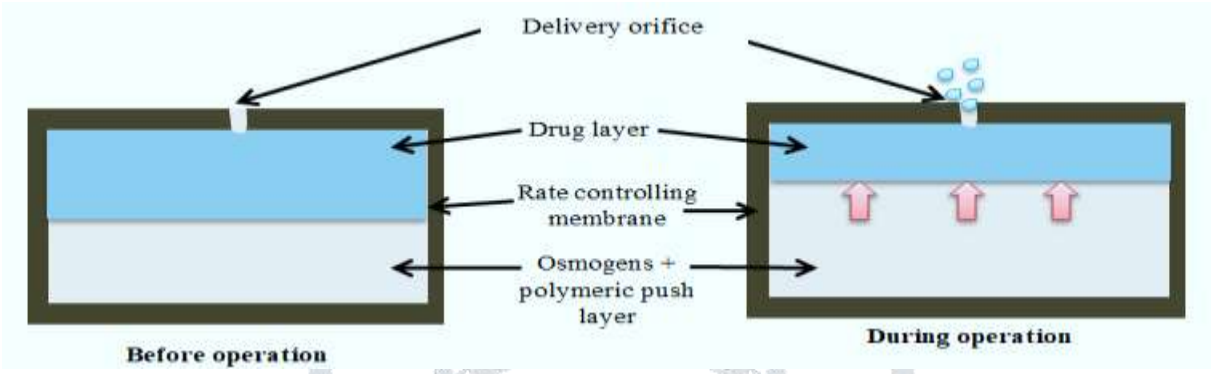

figure 5: push pull osmotic pump

2) Sandwiched Osmotic Pump

In this system an osmotic core of the tablet is composed of polymeric push layer sandwiched between two drug layers with two delivery orifices on different sides which is shown in fig 6. The middle polymeric push layer containing a swelling agent, swells as this system comes in contact with aqueous environment as a result drug is delivered in a controlled way from two orifices located on opposite sides of the tablet. Major limitation of this system, the delivered drug causes local irritation to the gastric mucosa.(4)(10)

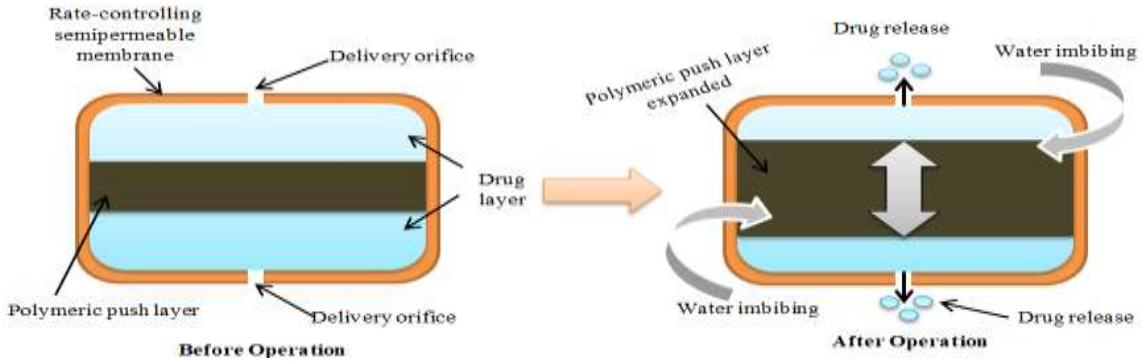

figure 6: sandwiched osmotic pump

3) Osmotic Pump With Non-Expanding Second Chamber

This is a another type of multi chamber osmotic pump with non expanding second chamber is present in it. Depending upon the role of second chamber, this system can split into two groups. In one group of these system, the second chamber is used to dilute the drug solution leaving the devices. This is beneficial because in some cases, saturated solution of drug causes irritation to the of GI tract and it is so risky. This type of system consist of two rigid chamber, the first chamber containing a biologically active inert osmotic agent, such as sugar or a simple salt like NaCl, the second chamber contains the drug. In this system water is enters into both chamber through the

surrounding semi-permeable membrane. In the first chamber, solution of osmotic agent formed then it is passes towards the drug chamber through the hole**,** where it mixes with the drug solution before leaving through the micro porous membrane that form a part of wall surrounding the chamber. The device is only suitable to delivered insoluble drugs.[2][13]

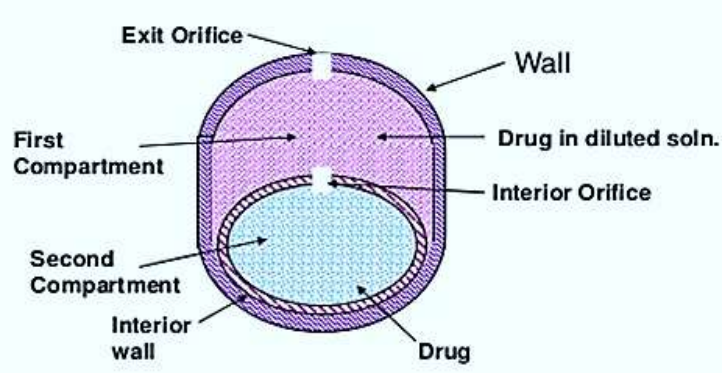

figure 7:osmotic pump with non-expanding second chamber

3. Specific Types

1) Controlled Porosity Osmotic Pump

Controlled porosity osmotic pump (CPOP) is a specific type of osmotic device wherein a water soluble pore forming agent incorporated in a semi-permeable membrane (such as urea, nicotinamide, sorbitol) which forms a delivery orifices by in-situ formation which is shown in fig. The release rate of drug from such system depends on various factors such as coating thickness, water permeability through semipermeable membrane, solubility of drug, level of leachable pore forming agent and osmotic pressure difference across the membrane, independent of pH, agitation of release media & so on. This device is economical because no laser drilling machine is required to form orifice.[15][16]

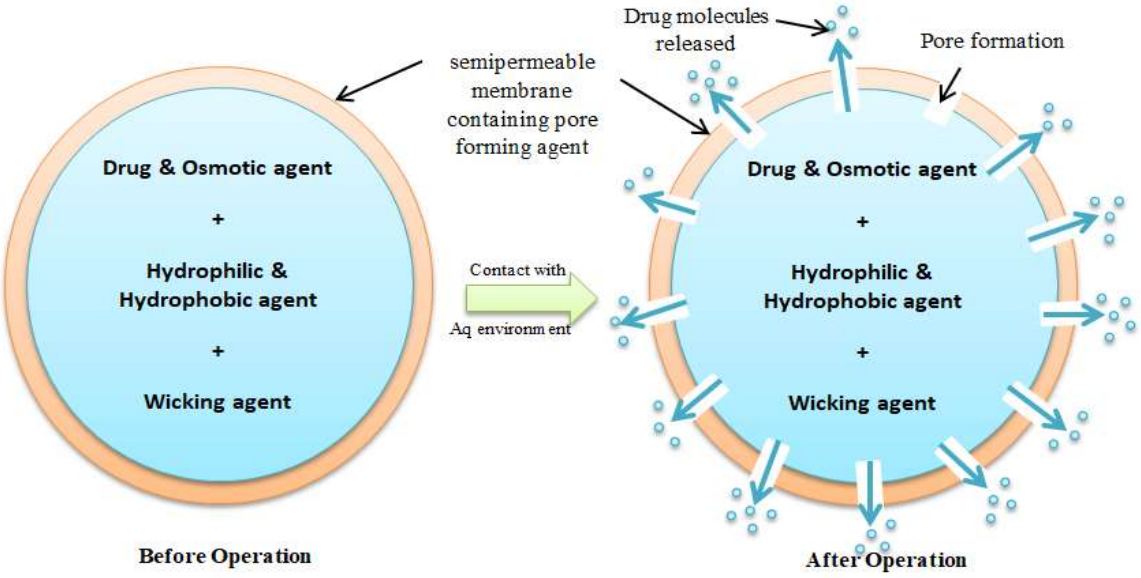

figure 8: controlled porosity osmotic pump

2) Osmotic Bursting Osmotic Pump

This system is much similar to an elementary osmotic pump, only the delivery orifice is absent and size of the device may be smaller. When this device comes in contact with aqueous environment, water is penetrated through the semi-permeable membrane and hydraulic pressure is built up inside core of device as a result, semipermeable membrane get ruptured and delivered the drug. The drug release from such system are mostly depend on thickness of the semi-permeable membrane. This system is useful to provide pulsated release.[17]

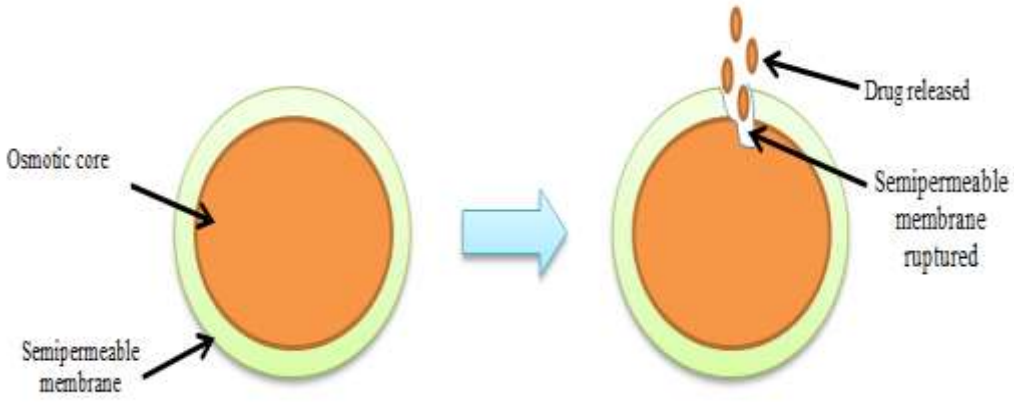

figure 9: osmotic bursting pump

3) Liquid OROS

Liquid OROS system is designed to deliver liquid drug formulations such as lipophilic self-emulsifying formulation (SEF) in a controlled manner to improve the bioavailability of drug. They are of three types: -

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

This osmotic device contains three layers i:e liquid drug layer, polymeric push layer and rate-controlling semipermeable membrane. When this osmotic device comes in contact with the aqueous environment, which activate the osmotic layer by water penetrating through the rate controlling membrane. The expansion of the osmotic layer results in the development of hydrostatic pressure inside the system, thereby forcing the liquid formulation to be delivered from the delivery orifice at controlled rate. This system is suitable to deliver insoluble drugs in aqueous fluids and is reported to increase the permeability of the drugs.[1][7][10]

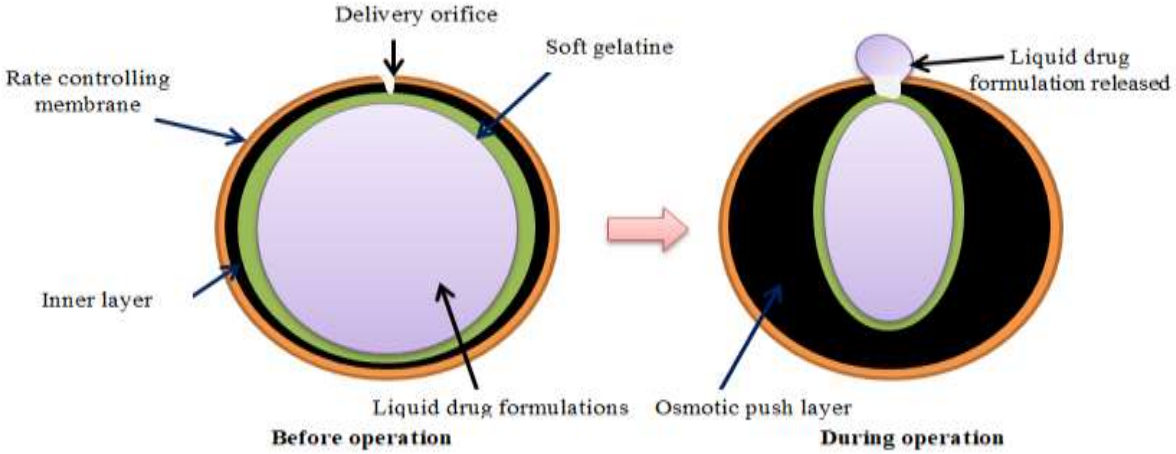

figure 10: liquid OROS

4) Monolithic Osmotic Pump Tablet

This is a simplest osmotic pump which contains a simple dispersion of water soluble drugs which is present in polymeric matrix form. When this osmotic pump comes in close contact with the aqueous environment, water is penetrating through the membrane and activate the agents which is incorporated into that device. This results, the polymeric matrix capsule get ruptured, surrounding by the drug, as a result water soluble dispersion of drug released in controlled manner into the outside environment. This process initially occurs in the polymeric matrix's outer

environment, but eventually progresses in a serial way towards the inside of the matrix. However this osmotic pump is not suitable if more than 20 to 30 volume/litre of active agent is incorporated into that device.[18]

5) Colon Targeted Oral Osmotic System

This osmotic pump is very useful for targeted delivery of drug to he colonic region and which can use for once or twice a day. This osmotic system is coated with 5-6 enteric coated polymer which can prevent the entry GI fluid from the stomach and push-pull osmotic units filled in hard gelatine capsule for targeting the drug to the colonic region which is shown in below fig. When this osmotic pump comes in close contact with GI fluid, the outer part of enteric coated polymer prevent the entry of fluid from the stomach, but later on gelatine capsule shell get dissolves after coming in contact with GI fluids of intestine as a result water is enters into the core and push the drug outside the environment through the orifice at predetermined rate.[19]

6) Asymmetrical Membrane Osmotic Tablet

Asymmetric membrane capsules consist of a core-containing drug surrounded by a membrane that has an asymmetric structure, that is a relatively small, dense region supported by a thicker, porous region. Unlike a conventional gelatine capsule, the capsule wall of asymmetrical membrane is made from insoluble polymer, which can not be dissolve immediately but provides prolonged release of the active ingredient incorporated in the capsule.[20]

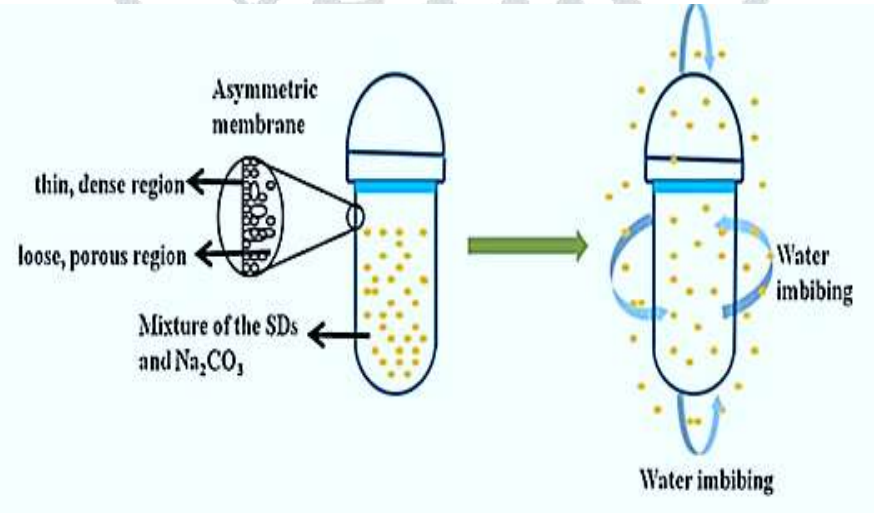

figure 11: asymmetrical membrane osmotic tablet

7) Telescopic Capsule For Delayed Release

This osmotic system consists two chamber in which first chamber contains drug and an exit port, second chamber contain an osmotic engine and these two chambers are separated by a wax like material. The required active agent is inserted in one of the parts of this osmotic system through manual or automated filling mechanisms. The bilayer tablet with the osmotic engine is placed into a completed cap part of the capsule with the convex osmotic layer pointed in to the closed end of the cap and the barrier into the closed end of the cap and the barrier layer exposed towards the cap opening. The open end of the filled vessel is fitted inside the open end of the cap, and the two pieces are compressed.[1][10]

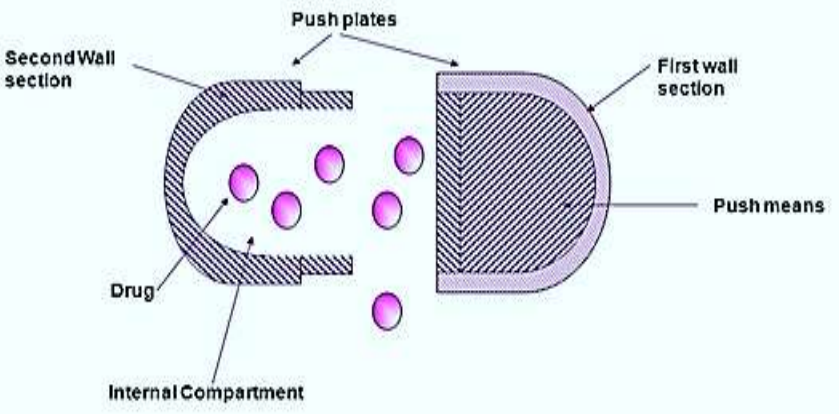

figure 12: telescopic capsule for delayed release

8) Multi Particulate Delayed Release System (Osmotic Pellets)

In this osmotic system, first pellets containing pure drug with or without osmotic agent are prepared and then it is coated with a semipermeable membrane such as cellulose acetate. When this osmotic device comes in close contact with the aqueous environment, water enters into the osmotic core and dissolve the osmotic agent, drugs and forms a saturated solution of drug. The osmotic pressure gradient across the membrane induces a water influx, leading to rapid expansion of the membrane and formation of the pores to the membrane, as a result saturated solution od drug release in a controlled manner and which follows nearly zero order kinetics.[21][22]

9) Effervescent Osmotic Pump Tablet

In this osmotic system, effervescent compound like sodium bicarbonate are inserted into the dosage form. When this osmotic pump comes in close contact GI fluid parts of stomach, the acid parts of stomach react with effervescent compounds and produce carbon dioxide. This CO_2 gas expands and dispenses the precipitate drug and prevents the blockage of orifice. This system is suitable to deliver poorly soluble drug at low pH because at this pH, drug gets precipitated and block the delivery orifice. Sodium bicarbonate is usually use in this system.[23]

10) Self-Emulsified Osmotic Tablet

In this osmotic system, self-emulsifying agent have been added in the osmotic core of the tablet and it is more suitable to deliver a slightly soluble or practically insoluble drugs. Generally self emulsifying agent are added to improves the bioavailability of drug because which can be deliver a drug in controlled manner and maintain the plasma concentrations more stable. It emulsifies the hydrophobic drugs. Typical different surface active agents such as poly-oxyethylenated glyceryl recinoleate, polyoxyethylenated castor oil having ethylene oxide, glyceryl laureates, glycerol (sorbiton oleate, stearate or laurate) have been used for this purpose.[10]

VII. BASIC COMPONENTS OF OSMOTIC SYSTEM

A. Drug

Generally all drugs are not an ideal candidate for osmotic system. A drug having short biological half life i:e 1 to 6 hours and which is used for prolonged treatment are an ideal candidate for osmotic system. Various drug candidates such as venlafaxine hydrochloride, diltiazem hydrochloride, carbamazepine, Glipizide, Metoprolol, Nifedipine, Verapamil, oxprenolol are suitable to deliver through the osmotic system. Drug having following characteristics are an ideal candidate for osmotic system.[2][4]

- It should have short biological half life.
- Prolonged release of drug should be desired.

- It should be potent in nature.
- Solubility of drug should not be very high and very low.

B. Osmotic Agent

Osmotic agent is an important components of osmotic system because release of drug depends upon osmotic agent used in the formulation, which create osmotic pressure inside the semipermeable membrane, when water is penetrate through semipermeable membrane and dissolve osmotic agent as result drug is delivered through the orifice in a controlled manner. Generally combination of osmotic agent are used to achieve desired osmotic pressure inside the core, but mannitol, sodium chloride and potassium chloride are most commonly used osmotic agents. Different types of osmotic agent are used in the osmotic system depending upon their properties and osmotic pressure build up, they are classified as.[(4)(10)]

- Water-soluble salt of inorganic acids such as Magnesium sulphate or chloride, sodium or potassium chloride, sodium or potassium hydrogen phosphate, sodium sulphate.
- Water-soluble salts of organic acids such as sodium and potassium acetate, Magnesium succinate, sodium ascorbate, sodium benzoate, sodium citrate.
- Carbohydrates such as Mannose, sucrose, maltose, lactose, etc.
- Water-soluble amino acids and organic polymer osmogens such as sodium carboxy methyl cellulose, Hydroxy propyl methyl cellulose, Hydroxy ethyl methyl cellulose, polyethylene oxide, Methylcellulose and polyvinyl pyrollidone.

C. Semi-permeable Membrane

Semi-permeable membrane is an important part of osmotic drug delivery system so the selection of polymer is based on solubility of drug, permeability, as well as amount and rate of drug to be released from osmotic system. Generally the polymers which are selected for osmotic system are permeable to water but impermeable to solute. Cellulose acetate is one of most commonly used semipermeable polymer for coating the osmotic core of the tablet because it is available in different grades. Cellulose acetate is available in a wide range of acetyl content, chain lengths and thus on its molecular weights. Particularly, acetyl content of 32% and 38% is mostly preferred. A different polymers used as semipermeable coating to the osmotic tablet are cellulose esters such as cellulose acetate, cellulose diacetate, cellulose triacetate, cellulose propionate, cellulose acetate butyrate, and cellulose ethers like ethyl cellulose**.** In addition to cellulose derivatives, several other polymers such as amylose triacetate, betaglucan acetate, poly(vinyl methyl) ether copolymers, poly(orthoesters), poly acetals and selectively permeable poly(glycolic acid), poly(lactic acid) derivatives, and Eudragits can be used as semipermeable coating agents. The selection of polymer for the semipermeable coating to the tablet, permeability is an important consideration taking into account. The polymers which are selected for the osmotic tablet as a semi-permeable coating agent meets following characteristics.[(24)(25)]

- It should be permeable only to the water.
- It should be stable to withstand pressure generated inside the osmotic device.
- It should be biocompatible.
- It should be rigid and non-swellable.
- It should have adequate wet strength and water permeability.

D. Plasticizer

In the osmotic system, the function of plasticizer is so important in modifying the physical properties and improving the polymer film forming characteristics. Plasticizer can improve the visco-elastic properties of polymer and increases it's work ability, flexibility, fluid permeability. Generally from 0.001-50 parts of plasticizer or a mixture of plasticizer are integrated into the 100 parts of coating materials. Plasticizer used in osmotic system are give below.[(2)(10)]

- Polyethylene glycol.
- Ethylene glycol monoacetate and diacetate for low permeability.
- Tri-ethyl citrate, Tri-ethyl phosphate.
- Diethyl tartarate or Diacetin for more permeability.

E. Hydrophilic & Hydrophobic Polymers

Generally this type of polymers are used in the development of osmotic controlled release formulations, in which drugs are present in matrix core. In hydrophobic matrices, extremely water soluble compounds can be co-entrapped and moderately water soluble compounds can be co-entrapped in hydrophilic matrices to obtain more regulate release. Generally, in case of development of osmotic tablet of water soluble drugs, the mixtures of both hydrophilic and hydrophobic polymers have been used to achieve more controlled release. The selection of polymer for the development of osmotic tablet, solubility of the drug as well as the amount and rate of drug to be released from osmotic pump is taking into the consideration because polymers which are either swellable or non-swellable in nature. Generally, most of the times swellable polymers are selected to deliver a moderately water-soluble drugs from the osmotic pumps because this type of polymers which increases the hydrostatic pressure inside the pump due to their swelling nature and vice versa the non-swellable polymers are used in case of highly water-soluble drugs. To achieve more controlled release of drugs from the osmotic tablet, ionic hydrogels such as sodium carboxy methyl cellulose have been used because of their osmogenic nature.[(24)]

- Examples of hydrophilic polymers such as hydroxy ethyl cellulose, carboxy methylcellulose, hydroxy propyl methylcellulose, high-molecular-weight poly(vinyl pyrrolidone).
- Examples of hydrophobic polymers such as ethyl cellulose and waxy materials.

F. Wicking Agent

A wicking agent characterized as a material with has capacity to draw water into the semipermeable membrane of the delivery device. The wicking agents are used is formulation of osmotic tablet to improve the contact surface area of the drug with the incoming aqueous fluid & it also helps to enhance the rate of drug released from the orifice of osmotic system. Wicking agents used in formulation of osmotic tablets are either swellable or non-swellable in nature. Examples are colloidal silicon dioxide, PVP and Sodium lauryl sulphate.[(13)]

G. Pore-forming Agent

In case of controlled porosity osmotic pump or multi-particulate osmotic pump, pore forming agent is an important component's of this osmotic pump because which can deliver a poorly water-soluble drugs in a controlled manner by in-situ formation inside the osmotic core as a result drug is delivered through the micro porous membrane formed by pore forming agent. The pore-forming agents which are organic or inorganic and solid or liquid in nature. Examples are given below.(10)

- Alkaline metal salts such as sodium chloride, potassium chloride, potassium sulphate, sodium bromide, potassium phosphate, etc.
- Alkaline earth metals such as calcium chloride and calcium nitrate.
- Carbohydrates such as sucrose, glucose, lactose, fructose, mannose, sorbitol, and mannitol.
- Polyols such as poly hydric alcohols, polyethylene glycols, and polyvinyl pyrrolidone.
- Tri-ethyl citrate (TEC) and triacetin.

H. Flux Regulators

Flux regulators are the agent which are used in the formulation & development of osmotic tablet because which regulate the permeability of fluids. Hydrophilic materials such as polyethylene glycol (300 to 6000 Da), polyhydric alcohols, polyalkylene glycol improves flow of fluids while flow is reduced by hydrophobic materials such as diethyl phthalate or dimethoxy ethyl phthalate.[5]

I. Coating Solvent

Coating solvent is an another important component's of osmotic system so, it's selection is depending upon the polymers which are used in the formulations because polymeric solution forma a semipermeable membrane. Coating solvents which are selected for formulation of osmotic tablet are given below.[24]

- Examples of coating solvents are methylene chloride, acetone, methanol, ethanol, isopropyl alcohol, butyl alcohol, ethyl acetate, cyclohexane, carbon tetrachloride, and water.
- Sometimes the mixture of solvents in given ratio form haven been used as a coating solvent 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).

VIII. FACTORS AFFECTING ON RELEASE OF DRUG FROM OSMOTIC SYSTEM

Following factors which affects on release characteristic of drug from osmotic system have been briefly explained below one by one.

A. Solubility

Solubility is a one of the major factor which affects on release characteristic of drug from osmotic system, so the drug which is selected to design a osmotic tablet should have sufficient solubility in water to achieve desired release rate from osmotic system. In case of low solubility drug in water, several alternative approaches have been used to modify the release rate of drug from osmotic system and they are given below.[2][26]

- Use of swellable polymers: Vinyl acetate co-polymer, polyethylene oxide
- Use of Wicking agent: Colloidal silicon dioxide, sodium lauryl sulphate.
- Use of solubility enhancers: Cyclodextrin.

B. Size Of Delivery Orifice

Size of orifice is an important factor to be consider before making a delivery orifice to the coated tablet because release rates are directly proportional to its size. To achieve controlled release of drug from osmotic tablet or drug that follows an optimal zero order delivery profile, the cross sectional area of the orifice must be smaller than a maximum size to minimize drug delivery by diffusion through the orifice. Furthermore, size of orifice must be sufficient to deliver a drug in a controlled way i:e it must be above a minimum size or below the maximum.

Generally orifice size of the osmotic tablet ranges from 600µ to 1 mm. A different techniques/methods are used to make a delivery orifice to the osmotic tablet shown in below.[2][14]

- By using mechanical drilling.
- By using laser drilling machine: This technique is one of best to make a desired delivery orifice to the coated tablet because it is well established method for producing sub-millimetre size hole to tablets. Normally, carbon dioxide laser beam is employed for drilling purpose, that offers outstanding reliability characteristics at low costs.
- Use of Cyclodextrin derivatives as a solubility enhancer to improve the release characteristics of poorly water soluble drugs from osmotic system.
- Use of substitute salt form: Change in salt form of may change solubility.
- Use of encapsulated excipients: Solubility modifier excipient used in form of mini-tablet coated with rate controlling membrane.
- Resin Modulation approach: Ion-exchange resin is an another approach which is commonly used to modify the solubility of drugs. Resins which is used in osmotic formulations are Poly (4-Vinyl Pyridine), citric and adipic acids.
- Use of crystal habit modifiers: Generally drugs that are available in different crystal form shows different solubility, so those excipients are selected which may change the crystal habit nature of the drug, to modulate solubility characteristics of drug and this is done by Co-compression of drug with excipients. Different excipients which are selected to modulate the solubility of APIs by different mechanisms like saturation solubility, pH dependent solubility. Examples are as follows: Organic acids, Buffering agent, etc.

C. Osmotic Pressure

Osmotic pressure is an important factor which affects on release characteristic of drug from osmotic tablet because release rate of drug from osmotic formulations are directly proportional to the osmotic pressure generated by osmotic agent inside the osmotic core of the tablet. To maintain a zero-order release rate of drug from osmotic tablet, it is so important to keep the osmotic pressure constant inside the core because which can deliver a saturated drug solution in a controlled manner through the orifice. Sometimes combination of osmotic agent is used to achieve a desired osmotic pressure inside the osmotic core. Examples are given below.[27]

Table 2: examples of different osmotic agents having their different osmotic pressure have been listed in this table[5]

Compound or mixture	Osmotic pressure (atm)	Compound or mixture	Osmotic pressure (atm)
Lactose-Fructose	500	Mannitol-Sucrose	170
Dextrose-Fructose	450	Sucrose	150
Sucrose-Fructose	430	Mannitol-Lactose	130
Mannitol-Fructose	415	Dextrose	82
Sodium chloride	356	Potassium sulphate	39
Fructose	335	Mannitol	38
Lactose-Sucrose	250	Sodium phosphate tribasic. 12H2O	36
Potassium chloride	245	Sodium phosphate dibasic. 7 H2O	31

Lactose-Dextrose	225	Sodium phosphate dibasic. 12 H2O	31
Mannitol-Dextrose	225	Sodium phosphate monobasic. H2O	28
Dextrose-Sucrose	190	Sodium phosphate dibasic. Anhydrous	21

IX. EVALUATION OF OSMOTIC DRUG DELIVERY DOSAGE FORM[1][2]

A. Evaluation of powder and Blend

1. Bulk density
2. Tapped density
3. Compressibility index
4. Hausner's ratio
5. Angle of repose
6. Blend uniformity analysis
7. LOD/ Water by KF

B. Evaluation of osmotic tablet

1. Weight uniformity
2. Hardness
3. Thickness
4. Friability
5. Drug content/Assay
6. Content uniformity
7. DT
8. In vitro dissolution study
9. Effect of pH on drug release
10. Effect of osmotic pressure on drug release
11. Effect of diameter size and depth of orifice on drug release
12. Stability study as per ICH guideline
13. Release kinetics (first order, zero order, Higuchi plot, Korsmeyer–Pappas plot)

X. MARKETED PRODUCTS/ BRANDS[7][8][9][24]

Table 3: marketed products/brands under the category of osmotic drug delivery system

Sr. No	Product Name	Active ingredient	Design system	Dose (Mg)	Use
1	Acutrim	Phenylpropanolamine	EOP	75	Nasal decongestant
2	Alpress LP	Prazosin	Push-pull	1-5	Hypertension
3	Cardura XL	Doxazosin	Push-pull	4,8	Hypertension & enlarged prostate
4	Chronogesic	Sufentanil	Implantable	----	Opioid analgesic
5	Concerta	Methylphenidate	Implantable	18,27,36,54	ADHD and narcolepsy
6	Covers HS	Verapamil	Push-pull	180,240	Angina, Hypertension

7	Ditropan XL	Oxybutinin Chloride	Push-pull	5 to up to 20	antispasmodic and anticholinergic agent
8	Dynacirc CR	Isradipine	Push-pull	5,10	Hypertension
9	Effexor	Venlafaxine hydrochloride	EOP	37.5,75,150,225	Anti-depressant
10	Efidac 24	Chlorpheniramine maleate	EOP	4mg IR, 12mg CR	Used as antihistamine
11	Glucotrol XL	Glipizide	Push-pull	2.5,5,10	Anti-diabetics
12	Invega	Paliperidone	Push-pull	1.5,3,6,9	Schizophrenia
13	Minipress XL	Prazosin	EOP	2.5,5	Hypertension
14	Procardia XL	Nifedipine	Push-pull	30,60,90	Hypertension angina and heart attack
15	Sudafed 24	Pseudoephedrine	Push-pull	240	Nasal decongestant
16	Tegretol XR	Carbamazepine		100,200,400	anticonvulsant
17	Viadur	Leuprolide acetate	Implantable	65	prostate cancer
18	Volmex	Albuterol	Push-pull	4,8	Bronchodilator

XI. SCIENTIFIC STUDY

In this scientific study, different research articles have been include for better understanding the types osmotic drug delivery system.[14][15][18][20][21][28][29][30]

table 4: different research articles

Sr. No	Title Of Research Article	Authors	Type Of Osmotic System	Drug Candidate
1	Development, Evaluation, & Influence Of Formulation And Process Variables On In-Vitro Performance Of Oral Elementary Osmotic Device Of Atenolol	Arjun, et al	Elementary Osmotic System	Atenolol
2	Development And Evaluation Of Elementary Osmotic Pump Of Highly Water Soluble Drug: Tramadol Hydrochloride	Pramod kumar, et al	Elementary Osmotic System	Tramadol HCl
3	Development Of An Oral Push–Pull Osmotic Pump Of Fenofibrate-Loaded Mesoporous Silica Nanoparticles	Zhao, et al	Push–Pull Osmotic Pump	Fenofibrate
4	Development and Evaluation of Sandwiched Osmotic System Of Isoxsuprine Hydrochloride	Vikrant Suryavanshi, et al	Sandwiched Osmotic Pump	Isoxsuprine Hydrochloride
5	Development of Monolithic Osmotic Pump Tablet System for Isosorbide-5-Mononitrate Delivery and Evaluation of	X. Duan, et al.	Monolithic Osmotic Pump System	Isosorbide-5-Mononitrate

	it In Vitro and In Vivo			
6	Cellulose Acetate 398-10 Asymmetric Membrane Capsules for Osmotically Regulated Delivery of Acyclovir	Alka Sonkar, et al	Asymmetric Membrane Capsule Osmotic Pump	Acyclovir
7	Design And Development Of Controlled Porosity Osmotic Tablet Of Diltiazem Hydrochloride	Shahi, et al	Controlled Porosity osmotic Pump	Diltiazem Hydrochloride
8	Formulation And Process Optimization Of Multiparticulate Pulsatile 2 Q1 System Delivered By Osmotic Pressure-Activated Rupturable Membrane	S.-F. Hung, et al	Multiparticulate Pulsatile System Delivered By Osmotic Pressure-Activated Rupturable Membrane	Omeprazole, Omeprazole sodium and propranolol HCl

CONCLUSION:- From present study & from the extensive literature survey, it is concluded that, osmotic drug delivery system is most promising approach to develop an oral controlled release formulation for prolonged treatment diseases which can improve therapeutic effectiveness and minimizing side effects.

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