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# **Review** Article

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Corresponding Author

\* Nityanand S. Zadbuke,

Department of Pharmaceutics, Yash Institute of Pharmacy, Aurangabad -431134, Maharashtra, India.



Email: nityanandzadbuke@gmail.com

# Osmotic Controlled Drug Delivery Systems: An Overview

Sadhana Shahi<sup>1</sup>, Nityanand Zadbuke<sup>2\*</sup>, Ajit Jadhav<sup>1</sup>, Santosh Borde<sup>1</sup>

# ABSTRACT

Osmotic controlled drug delivery systems utilize the principles of osmotic pressure for the controlled delivery of active agent. The delivery rate of zero-order is achievable with these systems. The release rate from these systems is highly predictable and can be programmed by modulating the release control parameters. The drug release from these systems is independent of gastric pH and hydrodynamic conditions. A high degree of in vivo-in vitro correlation (IVIVC) is obtained with osmotically controlled drug delivery systems. In this review various types of osmotic systems, basic components, patent literature and commercially marketed osmotic drug delivery systems are discussed.

**Key-words:** Osmotic drug delivery system, Osmotic pressure, Zero order release rate, Semipermeable membrane, Laser drill.

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1. Department of Pharmaceutics, Government College of Pharmacy, Aurangabad - 431005, Maharashtra, India 2. Department of Pharmaceutics, Yash Institute of Pharmacy, Aurangabad - 431134, Maharashtra, India.

# INTRODUCTION

Oral osmotic drug delivery system (OODS) is most admired amongst the all other oral drug delivery system. Conventional oral drug delivery system releases the drug immediately which cannot release drug in controlled manner and effective concentration at target site. The release and bioavailability of drugs from these formulations depends on the factors such as physicochemical properties of drug, presence of excipients, presence of food, gastrointestinal (GI) pH and GI motility. To conquer this constraint a drug can be formulated in matrix, reservoir or osmotic systems. Oral osmotic drug delivery system is based on the principle of osmosis, which uses osmotic pressure as driving force to release the drug in controlled manner. OODS usually consists of a core including the drug, an osmotic agent, other excipients and semi permeable membrane coat with leachable pore forming agent.<sup>[1,2</sup>

#### Osmosis and its principle

Osmosis refers to 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 semipermeable membrane.<sup>3-5</sup>

The first osmotic effect was reported by Abbe Nollet in 1748 (Table 1). In 1877, Pfeffer performed an experiment using semipermeable membrane to separate sugar solution from pure water. In 1886, Vant Hoff identified the relationship between osmotic pressure, concentration and temperature. He discovered that osmotic pressure is proportional to concentration and temperature and the relationship can be described by following equation,

 $\Pi = \emptyset c RT$ 

Where,  $\Pi$  = Osmotic pressure

 $\emptyset$  = 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.<sup>6-8</sup>

Table 1: Development of Osmotic Drug Delivery System (ODDS)		
Year	Historical aspect of osmotic drug delivery system	
1748	First report of osmosis	
1877	Quantitative measurement of osmotic pressure	
1955	First osmotic pump by Rose-Nelson developed pump for	
	pharmaceutical research	
1973	Higuchi- Leeper introduced a new version of Rose-Nelson pump with certain modification	
1973	Osmotically powdered agent dispense device with filling means	
1975	Introduced the first oral osmotic pump i.e. EOP. It was the major	
	the major mile stone in the field of oral osmotic drug delivery	
	system.	
1976	Patent granted on the design of Alzet osmotic pumps which later extensively used as an experimental research tool in laboratory	
1979	Osmotic hursting drug delivery device	
1982	Patent issue for an osmotic system which consist of a layer of a	
1702	fluid swell able hydro gel to deliver insoluble to very insoluble to	
	verv insoluble drug.	
1984	First report of combination therapy by use of push pull osmotic	
	pump.	
1985	Controlled porous osmotic pump was developed from which drug	
	is leached out from the coating, eliminating the need of	
	complicated laser drill procedure.	
1986	Patent issue claiming a delivery system for controlled	
	administration of drug to ruminants.	

1989	Developed of Push Pull osmotic pump of Nifedipine (Procardia		
	XL) by Pfizer which was the largest selling cardiovascular product		
	in US market until 1995.		
1995	Patent to an osmotic dosage form for liquid drug delivery .The		
	system consist of an outside semi permeable wall, middle osmotic		
	active layer, capsule containing an active agent and an orifice for		
	delivery of the agent.		
1999	Asymmetric membrane capsule is introduced to deliver the drug		
	through the osmotic pressure.		
2000	DUROS Leurpolid implants i.e. Viadur approved as first		
	implantable osmotic pump for human by US FDA.		
2001	Patent granted for dosage form comprising liquid drug		
	formulation that can self-emulsify to enhance the solubility,		
	dissolution, & bioavailability of drug.		
2003	First report osmotic floating system.		

# Advantages<sup>9-12</sup>

- 1. Ease to formulate.
- 2. The zero-order drug release rate is achievable.
- 3. Drug delivery is may be delayed or pulsed.
- 4. Drug release rate is independent on gastric pH and hydrodynamic conditions of body.
- 5. The release rate of osmotic systems is highly predictable.
- 6. Enhanced patient compliance.
- 7. Reduced dosing frequency.

# Disadvantages13

- 1. High cost
- 2. Poor systemic availability
- 3. Dose dumping
- 4. Rapid development of tolerance
- 5. Difficulty in retrieval of therapy
- 6. It may cause irritation due to release of saturated solution of drug.
- 7. Special equipment is required for making an orifice in the system.

# CLASSIFICATION

I. Implantable osmotic pump

- 1. The Rose and Nelson pump
  - 2. Higuchi Theeuwes pump
- 3. Implantable Mini osmotic Pump
- II. Oral osmotic pump
- A) Single chamber osmotic pump
  - 1. Controlled porosity osmotic pump (CPOP)
  - 2. Elementary osmotic pump (EOP)
- B) Multiple chamber osmotic pump
  - 1. Osmotic pump with non-expanding second chamber
  - 2. Push- pull osmotic pump (PPOP)
- C) Modified Oral Osmotic Drug Delivery Systems (OODDS)
  - 1. Osmotic bursting osmotic pump
  - 2. Delayed delivery osmotic pump
  - 3. Monolithic osmotic pump (MOTS)
  - 4. Sandwiched osmotic tablets (SOTS)
  - 5. Osmotic matrix tablets (OSMATS)

- 6. Colon targeted osmotic pump (OROS-CT)
- 7. Liquid OROS controlled release system (L-OROS)
- 8. Osmotic Pellets (OP)
- III) Newer Technologies<sup>14</sup>
  - 1. Ensotrol Technology
  - 2. Portab System (Andrx Pharmaceuticals)
  - 3. Zeros Tablet Technology (ADD Drug Delivery Technologies AG, Switzerland)
  - 4. The Port® System (Therapeutic system research laboratory Ann Arbor, MI, USA)
  - 5. DURIN Technology
  - 6. Volume amplifier delivery devices

# I. Implantable osmotic pump

# 1. The Rose and Nelson Pump

Around 75 years after the discovery of the osmosis principle, it was first applied in the design of drug delivery systems. It consists of three chambers, a drug chamber, a salt chamber and a water chamber. In which a semipermiable membrane is placed to separate a salt chamber from water chamber by a semipermiable membrane. The difference in osmotic pressure across the semipermeable membrane influences the movement of water towards salt chamber. The movement of water in salt chamber increases the volume of salt chamber due to which the latex diaphragm which divide the salt and water chamber moves and the drug is pumped out of the device (Figure 1). <sup>15,16</sup>



Figure 1: Rose and Nelson Pump

The kinetics of pumping from Rose and Nelson pump is given by equation-

dMt/dt = (dv/dt)C

Where, dMt/dt is the drug release rate,

dv/dt is the volume flow of water in to salt chamber,

C is the concentration of drug in the drug chamber.

# 2. Higuchi Leeper Pump

It consists of rigid housing and semipermiable membrane. In place of elastic diaphragm a layer of low melting waxy solid such as microcrystalline paraffin wax is used to separate drug and osmotic chamber (Figure 2). Modified- Leeper pump accommodated pulsatile drug delivery. The pulsatile release was achieved by production of a critical pressure at which the delivery orifice opens and releases the drug. It is mostly used in veterinary medicine. It is either swollowed or implanted in animal body for delivery of antibiotics or growth hormones.<sup>17,18</sup>



Figure 2: Higuchi Leeper Pump

# 3. Higuchi Theeuwes Pump

Higuchi Theeuwes pump is a device contains the rigid housing is made up of semipermiable membrane which withstand with the pumping pressure developed inside the device due to permeation of water. It consists of salt chamber and orifice for control the release of drug from device (Figure 3). A combination of citric acid and sodium bicarbonate placed in salt chamber with water, which generates carbon di oxide gas. This exert the pressure on the elastic diaphragm, delivers the drug from device. Osmotic pump of this form are available under trade name Alzet.<sup>19,20</sup>



**Figure 3: Higuchi-Theeuwes Pump** 

# 4. Implantable Mini Osmotic Pump

Implantable mini osmotic pump is made up of three concentric layers, drug reservoir, the osmotic sleeves and the rate controlling semipermiable membrane. Also the flow moderator is inserted into the body of osmotic device. The innermost compartment of drug reservoirs surrounded by osmotic sleeves, a cylinder containing high concentration of osmotic agent. When the system is placed in aqueous environment osmotic sleeves is covered by semipermiable membrane and water enters the sleeves through membrane, compresses the flexible drug reservoir and displaces a drug solution through flow moderator.<sup>4</sup>

# II. Oral Osmotic Pump

# A) Single Chamber Osmotic Pump

# 1. Controlled Porosity Osmotic Pump (CPOP)

It consists of tablet core having drug, osmogen and other additives, which is surrounded by semi permeable membrane with leachable pore forming agent.<sup>21</sup>

# Mechanism of Drug release

Water-soluble additives dissolve after coming in contact with water, resulting in an *in situ* formation of a microporous membrane. The resulting membrane is substantially permeable to both water and dissolved solutes and the mechanism of drug release was found to be osmotic (Figure 4). It is mainly used to overcome the need for complicated and expensive laser drilling.



Figure 4: Controlled Porosity Osmotic Pump (CPOP)

# 2. Elementary Osmotic Pump (EOP)<sup>22-25</sup>

Rose-Nelson pump was further simplified in the form of elementary osmotic pump, which made osmotic delivery as a major method of achieving controlled drug release. EOP (Figure 5) was invented by Theeuwes in 1974. EOP is the most basic device made up of a compressed tablet. The EOP consists of an osmotic core with the drug, surrounded by a semi permeable membrane. This membrane contains an orifice of critical size through which agent is delivered. The dosage form after coming into contact with aqueous fluids, imbibes water at a rate determined by the fluid permeability of the membrane and osmotic pressure of the core formulation. The rate of imbibitions of water is determined by the fluid permeability of the membrane and the osmotic pressure of the core, which is dispensed at controlled rate from the delivery orifice in the membrane. Normally EOP deliver 60 - 80 % of its content at constant rate but it has short lag time of 30-60 minute. It is applicable for moderately soluble drug.



Figure 5: Elementary Osmotic Pump (EOP)

# Limitations

- 1. SPM should be 200-300µm thick to withstand pressure
- 2. Thick coatings lower the water permeation rate.
- 3. Applicable mostly for water soluble drugs

# B) Multiple Chamber Osmotic Pump

# 1. Osmotic Pump with Non-Expanding second chamber

It is a type of osmotic pump containing non expanding second chamber. This type of devices consist of two rigid chamber, the first chamber contains a biologically inert osmotic agent, such as sugar or a simple salt like sodium chloride, the second chamber contains the drug. Water is haggard into both the chamber through the surrounding semi permeable membrane. The solution of osmotic agent formed in the first chamber then passes in the drug chamber through the connecting 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 could be used to deliver relatively insoluble drugs.<sup>1,4</sup>

# 2. Push-Pull Osmotic Pump (PPOP)<sup>26, 27</sup>

It consists of two compartments, Upper compartment (drug compartment) contains the drug along with osmotically active agents and Lower compartment (push compartment) contains the polymeric osmotic agents (Figure 6).





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# Drug release mechanism

When the dosage form comes in contact with the aqueous environment, both compartments absorb water simultaneously. Because the lower compartment is devoid of any orifice, it expands and pushes the diaphragm into the upper drug chamber, thereby delivering the drug via the delivery orifice. Deliver both highly water-soluble and practically water-insoluble drugs. e.g. Oxybutynin hydrochloride, Nifedipine, Glipizide.

# C) Modified Oral Osmotic Drug Delivery System

# 1. Osmotic Bursting Osmotic Pump

Osmotic bursting osmotic pump composed of tablet core contains drug with osmogen and coated with semipermeable membrane having water soluble additives similar to an EOP expect delivery orifice is absent and size may be smaller. When it is placed in an aqueous environment, water is imbibed and hydraulic pressure is built up inside until the wall rupture and the content are released to the environment (Figure 7). This system is useful to provide pulsated release.<sup>28</sup>



Figure 7: Osmotic Bursting Osmotic Pump

# 2. Monolithic Osmotic Pump (MOTS)

Monolithic osmotic pump is a simple dispersion of a water-soluble agent is made in a polymer matrix. Drug release occurs by water imbibitions due to the active agent takes place that ruptures the polymer matrix capsule surrounding the agent, thus liberating it to the outside environment. MOTS used for a water-insoluble drug was developed using gum arabic as the osmotic, suspending, and expanding agent.<sup>29, 30</sup>

# 3. Sandwiched Osmotic Tablets (SOTS)

Sandwiched osmotic tablets consist of tablet core consisting of a middle push layer and two attached drug layers are coated with a SPM. Drug release done by active pharmaceutical ingredient (API) coming in contact with the aqueous environment, the middle push layer containing swelling agent swells and the drug is released from the delivery orifices (Figure 8). It is used to delivers drug from two opposite orifices, rather from the single orifice of the PPOP.<sup>31</sup>



Figure 8: Sandwiched Osmotic Tablets (SOTS)

# 4. Osmotic Matrix Tablet (OSMAT)

It is a novel osmotically driven matrix system, which utilizes the property of hydrophilic polymers to swell and gel in aqueous medium forming a semi-permeable *in situ*.Release from such a matrix system containing an osmogen could

be controlled by the osmotic phenomenon. OSMAT thus judiciously combines both matrix and osmotic characteristics resulting in a quantum improvement in drug delivery from swellable matrix systems.<sup>32</sup>

# 5. Colon Targeted Osmotic Pump (OROS-CT)

OROS-CT is used as once or twice a day formulation for targeted delivery of drugs to the colon. It is a System with 5-6 enteric-coated push-pull osmotic units filled in hard gelatin capsule which is dissolves after coming in contact with GI fluids. Enteric coating on the system prevents entry of fluid from stomach to the system and it dissolves after entering into intestine. The water imbibes into the core and push compartment will swell. At the same time, the flowable gel is formed which is pushed out via delivery orifice at predetermined rate. Incorporation of the cyclodextrin-drug complex has also been used as an approach for delivery of poorly water soluble drugs from the osmotic systems e.g. Sulfo butyl ether-B cyclodextrin sodium salt serves as a Solubilizers and osmotic agent. (Figure 9). About 80% of the drug was delivered to the large intestine by OROS-CT.<sup>33-35</sup>



Figure 9: Colon Targeted Osmotic Pump (OROS-CT)

# 6. Liquid OROS Controlled Release System (L-OROS)

L-OROS encompasses two types i.e. *L-OROS Soft cap and L-OROS cap*. In Soft cap, Liquid drug formulation is present in a soft gelatin capsule, which is enclosed with the barrier layer, the osmotic layer, and the release rate-controlling membrane. In hard cap, it comprises of a liquid drug layer and an osmotic device, all enclosed in a hard gelatin capsule and coated with semipermeable membrane (Figure 10).



Figure 10: L-OROS Soft Capsule and L-OROS Hard Capsule

# Drug release mechanism

The enlargement of the osmotic layer results in the development of hydrostatic pressure, thus forcing the liquid formulation to break through the hydrated gelatin capsule shell at the delivery orifice. Water is imbibed across the semipermeable membrane, expanding the osmotic engine, which pushes against the barrier, releasing the drug through the delivery orifice. It is suitable for controlled delivery of lipophilic APIs.<sup>36</sup>

# 7. Osmotic Pellet (OP)37,38

Osmotic pellet is a new model of drug release by osmotic pumping and diffusion mechanism. Pellets coated with a semipermeable film developed 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.

# III) Newer Technologies<sup>14</sup>

# 1. Ensotrol Technology

The drug is mixed with solubility modifier like wicking agents. It increases the surface area creating network of channel inside the core.

# 2. Portab System (Andrx Pharmaceuticals)

PORTAB has an osmotic core, typically containing a water-soluble drug. The core includes a water soluble component and a continuous polymer coating. The purpose of the soluble agent is to expand the core and thereby create microporous channels through which the drug is released.

# 3. Zeros Tablet Technology (ADD Drug Delivery Technologies AG, Switzerland)

The technology is used for lipophilic drug. It comprises of drug, excipients, gel forming agents. When fluid imbibes gel formation occurs with certain viscosity drug suspension is formed pushed out through the orifice.

# 4. The Port® System (Therapeutic system research laboratory Ann Arbor, MI, USA)

This capsule has three parts an active drug with osmotic agents, a slid able partition and a immediate release drug These all are encased by a semi-permeable membrane. At the fluid entry drug with an osmotic agents gets expanded creating osmotic pressure directly push the slider made of non-swellable polymer plug causing immediate release of drug after a lag time. This is suitable for continuous delivery of drug. Example methylphenidate for the treatment of attention deficit hyperactivity disorder in school age children.

# 5. DURIN Technology

DURIN technology use biodegradable polyester like lactide glycolide co-polymer as an excipient mixed with the drug for implantable drug formulation. It can load up to 70-80% of drug. Wide variety of drugs including hydrophobic, hydrophilic drug can be used. These esters get degraded by hydrolysis after drug release and are fully absorbed by tissues. The drug and excipients are mixed formed into rods, fiber, tablet, For example, Zoladex- goserelin used for prostate cancer have been successfully developed implants in which the Membrane includes a pore forming agent that will leach out upon exposure to an aqueous environment, creating a micro porous membrane The DURIN technology has successfully achieved controlled, zero-order drug release for up to 6 months in vivo.

# 6. Volume Amplifier Delivery Devices

One of the limitations of controlled-release devices and especially with osmotic devices is the incomplete release of the drug. The release rate decreases after ~80% of the drug has been delivered. The use of volume amplifiers to deliver the entire drug contained in the system is disclosed in Patents US4331728 (1982) and US4203439 (1980). The device consists of a core, an SPM, and a delivery orifice. In addition to the drug and the osmogen, the compartment contains a volume amplifier to increase the amount of agent delivered from the system. The amplifier consists of a membrane surrounding a gas-generating couple with the membrane formed of an expandable material that is permeable to fluid and impermeable to the couple. In use, the active agent is delivered from the system through the passageway at a controlled rate because fluid is imbibed through the wall into the compartment to produce a solution-suspension of the drug. Simultaneously, the amplifier increases in volume (because of the generation of the gas) and fills the compartment, forcing the desired agent to be released at a rate controlled by the permeability of the wall, the osmotic pressure gradient across the wall, and the rate of imbibition's and increase in the amplifier's volume. The system completely delivers the drug at a non-falling rate. The gas-generation couple in a volume amplifier can be a mixture of an acid sub-stance and a base substance. The volume amplifier membrane is free of passageways and contains an expansion agent that gives the membrane flexibility and expandability. Elastomeric

materials used for this purpose include rubber, poly isoprene, poly isobutylene, poly butadiene, and ethylenepropylene copolymer.

#### BASIC COMPONENTS OF OSMOTIC CONTROLLED DRUG DELIVERY SYSTEMS Drug

All drugs are not suitable candidate for osmotic system as prolong action medication. Drug with biological half life > 12 hr (e.g. Diazepam) and drug which have very short half life i.e. <1 hr (e.g. Penicillin G, Furosemide) are not suitable candidate for osmotic controlled systems. Drug which have short biological half-life and which is used for prolonged treatment are ideal candidate for osmotic controlled systems. A variety of drug candidates such as Diltiazem hydrochloride, Carbamazepine, Metoprolol, Oxprenolol, Nifedipine, Glipizide etc. are formulated as osmotic controlled delivery.

# Semipermeable Membrane (SPM)

An important part of the osmotic drug delivery system is the SPM housing. Since the semipermeable membrane is permeable to water and not to ions, the release rate is essentially independent of the pH of the environment. Therefore, the polymeric membrane selection is key to osmotic delivery formulation. Some of the polymers that can be used for above purpose include cellulose esters such as cellulose acetate, cellulose diacetate, cellulose triacetate, cellulose propionate, cellulose acetate butyrate, and cellulose ethers like ethyl cellulose. Cellulose acetate is a commonly employed semi permeable polymer for the preparation of osmotic pumps.<sup>39</sup> The various polymers used as semipermeable membrane (SPM) and their water vapour transmission rates (WVTR) are summarized in Table 2. **Table 2: Polymers Used As Semipermeable Membrane and Their Water Vapour Transmission Rates (WVTR)** 

WVTR (g/100m <sup>2</sup> /24hr/mm thick)
100
70
40-75
50
30-100
75
1-3
>1.2
8
1-3
0.7

The membrane must possess certain performance criteria such as:

- 1. Sufficient wet strength and water permeability
- 2. Should be biocompatible
- 3. Rigid and non-swelling
- 4. Should be sufficient thick to withstand the pressure within the device

#### Osmogen<sup>40,41</sup>

Osmogen are essential ingredient of osmotic pump, usually ionic compounds consisting of either inorganic salts or hydrophilic polymers and carbohydrates. Osmogen are freely water soluble and capable of producing osmotic pressure. Osmogen maintain a concentration gradient across the membrane. They also generate a driving force for the uptake of water and assist in maintaining drug uniformity in the hydrated formulation. Generally combination of osmogen is used to achieve desired osmotic pressure within the device. Table 3 represents different osmogen and their osmotic pressure.

Osmogen	Osmotic Pressure of Saturated	
	Solution (Atmosphere)	
Lactose : Fructose	500	
Dextrose : Fructose	450	
Mannitol : Fructose	415	
Sodium chloride	356	
Fructose	355	
Potassium chloride	245	
Mannitol : Sucrose	170	
Sucrose	150	
Mannitol : Lactose	130	
Dextrose	82	
Citric acid	69	
Ascorbic acid	54	
Mannitol	38	
Lactose	23	

Table 3: Osmogen and	Their Osmotic Pressure

# Pore forming Agent

The 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 of the system. The pore formers can be inorganic or organic and solid or liquid in nature. It should be non-toxic, and on their removal, channels should be formed. Alkaline metal salts such as sodium chloride, sodium bromide, potassium chloride, 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, diols and polyols can be used as pore forming agents.<sup>1,5,10,12</sup>

# Wicking Agents

Wicking agents are the material used to draw water into the porous network of a delivery device. The function of the wicking agent is to increase contact surface area of drug with the incoming aqueous fluid. It helps to enhance the rate of drug released from the orifice of drug. It is available in swellable and nonswellable form. Colloidal silicon dioxide, kaolin, titanium dioxide, alumina, niacinamide, sodium lauryl sulphate (SLS), low molecular weight polyvinyl pyrrolidone (PVP), bentonite, magnesium aluminium silicate, polyester and polyethylene,etc. can be used as wicking agents<sup>42,43</sup>

# Coating Solvent<sup>44</sup>

The main function of coating solvent is to make polymeric solution which has important role in manufacturing the wall of the osmotic device include inert inorganic and organic solvents that do not adversely harm the core, wall and other materials.<sup>(1)</sup> the various types of solvents and their combinations are as follows: Methylene chloride, methanol, isopropyl alcohol, di-chloromethane, ethyl acetate, acetone, carbon tetrachloride, cyclohexane, butyl alcohol, water etc. and the mixture of solvents such as acetone-methanol(80:20), methylene chloride-methanol(79:21),acetone-ethanol(80:20).

The ideal properties of solvents:

1. It should easily and completely dissolve the polymer.

2. It should easily disperse other coating components into solvent system.

3. It should not give extremely viscous solution with small concentration of polymer (2-10%) because it create process problem.

4. It should be odourless, colourless, tasteless, inexpensive, nontoxic and non-irritant.

5. It should have rapid drying rate.

# Plasticizers45

Different types and amount of plasticizers used in coating membrane also have a significant importance in the formulation of osmotic systems. They can change visco-elastic behaviour of polymers and these changes may affect the permeability of the polymeric films. It lowers the temperature of the second order phase transition of the wall or the elastic modules of the wall and also increases the workability. Plasticizers can have a marked effect both

quantitatively and qualitatively on the release of active materials from modified release dosage forms where they are incorporated into the rate-controlling membrane. Generally from 0.001 to 50 parts of a plasticizer or a mixture of plasticizers are incorporated in to 100 parts of wall forming materials.

Some of the plasticizers used are polyethylene glycols, glycolate, glycerolate, myristates, ethylene glycol monoacetate; and diacetate for low permeability, tri ethyl citrate, diethyl tartarate or diacetin for more permeable films

# Flux regulators

Flux regulating or flux enhancing agent or flux decreasing agents are added to the wall forming materials. It assists in regulating the fluid permeability of flux through wall. This agent can be pre-selected to increase or decrease the liquid flux. They also increase the flexibility and porosity of lamina. Hydrophilic substances such as poly ethylene glycols (300 to 6000 Da), polyhydric alcohols, polyalkylene glycols,) and the like improve the flux, whereas hydrophobic materials such as phthalates substituted with an alkyl or alkoxy (e.g. diethyl phthalate or dimethoxy ethyl phthalate) tend to decrease the flux. Insoluble salts or insoluble oxides, which are substantially water-impermeable materials, also can be used for this purpose.<sup>46</sup>

# Solubilising agents

The types of solubilising agents are-

1) Solubilizers which obstruct crystal formation of the drugs or otherwise form complex with drug. Eg. PVP, poly (ethylene glycol) (PEG 8000) and alpha, beta gammacyclodextrins.

2) A high HLB micelle- forming surfactant, predominantly anionic surfactants. Eg. Tween 20, 60 and 80, poly oxy ethylene or polyethylene containing surfactants and other long chain anionic surfactants such as sodium lauryl sulphate (SLS)

3) Citrate esters and their combinations with anionic surfactants. Eg alkyl esters particularly tri ethyl citrate.

# KEY PARAMETERS THAT INFLUENCE THE DESIGN OF OSMOTIC CONTROLLED DRUG DELIVERY SYSTEMS Orifice size

Main stream of osmotic drug delivery systems contain at least one delivery orifice (preformed or formed in situ) for drug release in the membrane.<sup>[15</sup> To reduce drug delivery by diffusion all the way through the orifice, to accomplish an optimal zero order delivery profile, the cross sectional area of the orifice must be smaller than a maximum size. Furthermore, to minimize hydrostatic pressure build up in the system the area must be sufficiently large, above a minimum size. The emblematic orifice size in osmotic pumps ranges from 600µ to 1 mm.

# Methods to create a delivery orifice in the osmotic tablet coating are

# 1. Mechanical drill

Orifice is mechanically drilled in the centre of each pump. The aperture diameter and coating thickness is measured microscopically using empty shell obtained after complete dissolution of the contents.<sup>47</sup>

# 2. Laser drill<sup>48-50</sup>

Unlike traditional drilling, laser drilling to a limit is basically an advanced process of making precise & accurate holes by using a laser. Laser drilling machine is mainly used for making small and precise holes in numerous shapes and also in a comprehensive range of materials up to a thickness of 4-5mm. In laser drilling process, using a laser of high power ensures superior drilling of holes in many engine parts. Drilling of diamonds, pharmaceutical tablets, strainers, low filters and guide vanes are possible with the help of a well equipped laser drilling machine. Small diameter holes can be produced with the help of laser drill machine with the precise accuracy.

Laser drilling is well established as an economically viable method for producing submillimeter apertures in pharmaceutical tablets. A laser is used to form a precision orifice in the barrier. Since the barrier is permeable only to water, initial penetration of water dissolves the outer part of the core, resulting in the development of an osmotic pressure difference across the membrane.<sup>[51</sup> The benefits of sophisticated drug delivery systems are well proven, including decreased dosing frequency, more consistent drug concentration in the blood, and even customized delivery profiles<sup>[52.</sup> The main functional elements of a commercial, laser-based tablet drilling system are shown in Figure 11. This particular configuration utilizes two laser drilling stations and can drill either one or both sides of a tablet.



Figure 9: Laser Based Tablet Drilling System

Laser tablet drilling supports throughput rates of up to 100,000 tablets/hr, and can easily produce holes with the necessary dimensional tolerances and cosmetic appearance. As a result, laser drilling has become the technology of choice for this type of orifice production as well as other drug delivery systems whose operation is critically dependent on the presence of one or more small holes in the tablet coating

#### Laser Requirements

Virtually any type of industrial laser can produce holes with the sizes and tolerances required for tablet drilling. Therefore, the primary selection criterion for the laser source is the throughput speed it can support. Secondary considerations are factors such as operating costs and up time. The maximum achievable throughput speed for tablet drilling is influenced by several laser characteristics e.g. if all other factors are equal, throughput increases when using a laser whose output wavelength is well absorbed by the material to be processed. High absorption in the processed material also ensures that no significant laser power penetrates through to other layers in the delivery system, where it might cause damage.<sup>53-55</sup>

# 3. Use of modified punches

The dosage form is pierced using a piercing and unsheathed upon application of compression force. The coating powder to be compressed in charged to the die mold and unpierced tablet core is placed upon it. Additional quotation of coating powder is added to the die mod, subsequent to which both compression and piercing are done simultaneously.<sup>56</sup>

# 4. Use of leachable substances in the semi permeable membrane<sup>57-60</sup>

E.g. In controlled porosity osmotic pump the in situ pore formation takes place depending on the concentration of the pore-forming agent in the coating solution eg. NaCl, NaBr, KCl, CaCl<sub>2</sub>, calcium nitrate, sucrose, glucose, fructose.

# Solubility

Solubility is very important factor in the release rate depends on the solubility of the solute inside the drug delivery system. Solubility is directly proportional to the release kinetics from the osmotic system. Therefore, drugs should have sufficient solubility to be delivered by osmotic delivery. Drugs with high and low water solubility do not a good candidate for osmotic delivery. The solubility of drug in the core can be modified by incorporating appropriate solubility modulators to switch the release of drug from the osmotic system (Table 4).<sup>61, 62</sup>

# EVALUATION PARAMETERS OF OSMOTIC CONTROLLED DRUG DELIVERY FORMULATION63-67

Oral osmotic drug delivery systems can be evaluated by-

# Visual Inspection

Visual inspection of the film can be done for evaluating smoothness, uniformity of coating edge coverage and luster of osmotic drug delivery formulation.

Approaches	Mechanism
Use of wicking agent	It may enhance the surface area of drug with the
	incoming aqueous fluids.E.g. colloidal silicon dioxide,
	sodium lauryl sulfate, etc.
Resin Modulation approach	It is commonly used to modify the solubility of
	drugs.E.g. Poly(4-vinyl pyridine), Pentaerythritol, citric
	and adipic acids
Use of swellable polymers	Polymers such as vinyl acetate copolymer,
	polyethylene oxide causes drug release at constant rate
	because they have uniform swelling rate
Use of effervescent mixtures	Mixtures of citric acid and sodium bicarbonate which
	creates pressure in the osmotic system and ultimately
	controls the release rate
Use of cyclodextrin derivative	They are known to increase solubility of poorly soluble
	drugs. The phenomenon can also be used for the
	osmotic systems.
Use of alternative salt form	Change in salt form of drug may change solubility, as
	was reported for oxprenolol
Use of crystal habit modifiers	Different crystal form of the drug may have different
	solubility, so the excipient which may change crystal
	habit of the drug can be used

# Table 4: Approaches to Modify Solubility

# **Coating Uniformity**

The uniformity of coating amid the tablets can be assessed by determining the weight, thickness and diameter of the osmotic drug delivery tablet before and after the coating.

# Scanning Electron Microscopy

Coating membranes of formulation obtained before and after complete dissolution of core contents can be examined for their porous morphology by scanning electron microscope.

# Coat Weight and Thickness

The coat weight and thickness can be determined by exhausted devices following careful washing and drying of the film, using standard analytical balance and screw gauge, respectively.

# **Orifice Diameter**

The mean orifice diameter of osmotic pump tablet can be determined by using microscope with pre calibrated ocular micro meter.

# **Effect of Osmotic Pressure**

To confirm the major mechanism of drug release, release studies of the optimized formulation can be conducted in media of different osmotic pressure. To increase the osmotic pressure of the release media (pre-equilibrated to  $37^{\circ}C \pm 1^{\circ}C$ ), mannitol (osmotically effective solute) can be added.

# Effect of agitational intensity

To study the effect of agitation intensity (rpm) of the dissolution medium, the release study was carried out using USP dissolution apparatus) at different rotational speeds e.g. 50,75, 100, and 150 rpm using the dissolution medium (900 ml) or otherwise specified in the monograph.

# Effect of pH

In order to study the effect of pH and to assure a reliable performance of the developed formulations independent of pH, release studies can be carried out at different pH ranges e.g. pH 1.2 in simulated gastric fluid (SGF) and pH 6.8 in simulated intestinal fluid (SIF) and distilled water, etc.

# In vitro Drug Release

The in vitro drug delivery rate from osmotic systems can be determined by diverse methodologies, which consist of vertically reciprocating shaker, conventional USP dissolution apparatus I and II, flow-through apparatus, using distilled water as well as simulated gastric fluid (for 2-4 hr) and intestinal fluids for subsequent hours is used as a dissolution medium.

### Kinetics of Drug Release

The data obtained can be fitted in different models at different time intervals and by using statistics we can know kinetics of drug release

#### In Vivo Evaluation

Dogs have commonly been used for in vivo delivery rate measurement of drug(s) from oral osmotic delivery systems (OODS) and also to establish *in vitro /in vivo* correlation (*IVIVC*). As the environment terms of pH in the intestinal tract of the dog is quite similar to that of the human beings in and motility. In vivo evaluation can also be performed in healthy human volunteers. Various pharmacokinetic parameters (Cmax, Tmax, AUC and MRT) and relative bioavailability are calculated

#### **OSMOTIC DRUG DELIVERY SYSTEMS IN COMMERCIAL MARKET**

Development efforts of oral osmotic delivery systems (OODS) during recent years have been very dynamic with the emergence of new technologies and products. With the expiration of the OODS primary patents and the increasing demand of health authorities for improved patient treatment compliance and tolerability, the OODS is primed to increase their market within oral modified-release dosage forms. Developed as a drug delivery platform for delivering drugs regardless of their physicochemical properties, OODS have several applications (i) in early clinical phases (including early-stage exploration of pharmacokinetics), (ii) in novel dosage form development and (iii) in product life-cycle management. The clinical benefits of OODS mainly reside in their capacity to deliver a drug at a predetermined rate, independent of physiological parameters such as food intake or patient age. Nowadays, the large variety of OODS technologies available allows an interesting adaptation of the system to the drug properties and dosage strength. Despite the controversy concerning the safety in the administration of non-disintegrable tablets, the reported clinical benefits have opened up new perspectives to the future development of drugs as oral osmotically driven systems.

The number of patented marketed oral osmotic delivery systems (ODDS)<sup>68</sup> has doubled in the last 10 years (Table 5 and Table 6). Today, different types of osmotic pumps, of various drugs, are available in the market to meet patient's need and requirement. 53% of market was captured by with Johnson & Johnson (20 products), and 26% by Osmotica Pharmaceutical Corp. (10 products). Seven products are currently in the late development stage of clinical trial. These products cover primarily the following four therapeutic areas cardiovascular (35%), neurological (25%), seasonal (25%) and metabolic disorders (15%). The increasing number of marketed products has translated into a two fold increase in the ODDS revenues in the past 5 years, reaching about 3 billion dollars worldwide annual sales. Thus, the ODDS worldwide sales increased from about 3.0% of the modified-release forms in 2002 to 6.2% in 2012.<sup>69</sup>

Table 5: Important Patents Based On Osmotic Drug Delivery system
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System Type	Drug	Patent No.	Year
Elementary osmotic pump	Indomethacin	US4265874	1981
Elementary osmotic pump	Haloperidol	US4610686	1986
Elementary osmotic pump	Chlorpheniramine	US4857330	1989
Elementary osmotic pump	Nicotine	US5147654	1992
Elementary osmotic pump	Nystatin	US5776493	1998
Elementary osmotic pump	Levodopa	US5869096	1999
Second expandable osmotic chamber	Procainamide HCl	US4331728	1982
Second expandable osmotic chamber	Verapamil	US5156850	1992
Second expandable osmotic chamber	Zafirlucast	US6224907	2001
Multichamber osmotic system	Diltiazem HCl	US4859470	1989
Multichamber osmotic system	Tandospirone	US5185158	1993
Multichamber osmotic system	Glipizide	US5545413	1996

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Multichamber osmotic system	Captopril	US5976571	1999
Multichamber osmotic system	Captopril	US6207197	2001
Multichamber osmotic system	Nifedipine	US6352721	2002
Controlled porosity osmotic pump	Venlaflaxine/Metoprolol	US20100291208	2010
Push Pull Osmotic Pump	Paliperidone	US8920835 B2	2014
Controlled Porosity Osmotic Pump	Venlaflaxine/Metoprolol	US8703193 B2	2014
Push Pull Osmotic Pump	Felodipine	US9005661 B2	2015

Table 6: Marketed Osmotic Drug Delivery Systems			
Brand Name	API	Туре	Marketed By
UT-15C	Treprostinil diethanolamine	SEOP	United Therapeutics
LCP-Lerc	Lercanidipine	DOEOP	Osmotica/Recordati
Cardura CR	Doxazosin mesylate	PPOP	Alza/Pfizer
Concerta	Methylphenidate HCl	PSOP	Alza/McNeil
Ditropan XL	Oxybutynin chloride	PPOP	Alza/UCB Pharma
Teczem	Enalapril Diltiazem HCl	CPOP	Merck/Aventis
Tiamate Dilacor XR	Diltiazem HCl	CPOP	Merck/Aventis Andrx
Covera HS	Verapamil HCl	COER	Alza/Pfizer
DynaCirc CR	Isradipine	PPOP	Alza/Novartis
Minipress XL	Prazosin	PPOP	Alza/Pfizer
Procardia	Nifedipine	PPOP	Alza/Pfizer-Bayer
Topamax	Topiramate	PSOP	Alza
AltoPlus XR	Metformin/Pioglitazone	SCOT	2 Andrx/Takeda
Fortamet	Metformin HCl	SCOT	Andrx
Altoprev	Lovastatin	EOP	Andrx
Glucotrol XL	Glipizide	PPOP	Alza/Pfizer
Flexeril XL	Cyclobenzaprine	EOP	Alza
Oxycontin	Oxycodone	PPOP	Alza
Jusnista	Hydromorphone	PPOP	Alza/J&J
Invega	Paliperidone	PPOP	Xian–Janssen
Elafax XR	Venlafaxine HCl	EOP	Osmotica/Phoenix
Tegretol XL	Carbamazepine	SEOP	Alza/Novartis
Osmosin	Indomethacin	EOP	Alza/Merck
Teosona Sol	Theophylline	DOEOP	Osmotica/Phoenix
Allegra D 24 h	Pseudoephedrine /Fexofenadine	DOEOP	Osmotica/Aventis
Loremex	Pseudoephedrine/ Loratadine	DOEOP	Osmotica/Phoenix
Mildugen D	Pseudoephedrine /Astemizole	DOEOP	Osmotica/Phoenix
Efidac24	Brompheniramine/Pseudoephedrine	EOP	Alza/Novartis

EOP

EOP

DOEOP

Alza/Novartis

Alza/Novartis

GSK/Muro

Chlorpheniramine /Pseudoephedrine Pseudoephedrine HCl

Albuterol

Efidac24

Efidac24

Volmax

# CONCLUSION

In this review we have tried to provide guide to the osmotic controlled drug delivery systems. The osmotic drug delivery systems may be used to deliver drugs at a controlled rate over a period of 12-24 hr throughout the GI track. These systems deliver some drugs with short half-life, and which are to be given frequently for chronic ailments, in the form of controlled-release (CR) formulations. The delivery rate of zero-order is achievable with these systems. The release rate of osmotic systems is highly predictable and can be programmed by modulating the release control parameters. The release from osmotic systems is independent of gastric pH and hydrodynamic conditions

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