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Corresponding Author:

*** Ghanshyam Umaretiya,**
School of Pharmacy,
R. K. University,
Rajkot, Gujarat.
India.

Contact No.: +91 9909094759

*Email Id-
shyam.umaretiya@gmail.com

Osmotically Controlled Oral Drug Delivery Systems – A Review

Ghanshyam Umaretiya*, Dr. J. R. Chavda*, Dr. J. K. Patel**

ABSTRACT

Osmotic drug delivery systems are new approach for a modified release dosage form. Various innovations and patents available for various types of osmotic drug delivery system. The review is concerned with the drug release study of tablets coated with walls of controlled porosity. Drugs can be delivered in a controlled pattern over a long period of time by osmotic process. These devices are the most promising strategy and most reliable controlled drug delivery system as oral drug delivery systems. In this paper, mechanism of osmosis, principle of osmosis, factors affecting drug release, types of pumps and materials used, evaluation, various types of osmotic drug delivery systems and the basic components have been discussed briefly.

Key-words: Osmotic drug delivery, Formulation factors, Controlled dug delivery, Osmotic pump

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* Dr. J. R. Chavda : B.K. Modi Govt. Pharmacy College, Rajkot, Gujarat
** Dr. J. K. Patel, Nutan Pharmacy College, Visnagar, Gujarat

INTRODUCTION

In recent years, considerable attention has been focused on the development of novel drug delivery systems (NDDS) because of relatively low development cost and time required for introducing a NDDS as compared to a new chemical entity. Reason for development of NDDS is give a new life to existing molecules in the field of pharmaceutical development.

Oral controlled release (CR) systems hold the major market share because of their obvious advantages of greater effectiveness in the treatment of chronic conditions, reduced side effects, and greater patient convenience due to a simplified dosing schedule, ease of administration and better patient compliance [1].

Amongst number of design options are available to control or modify the release of drug from a dosage unit, most of per oral CR dosage forms cover under category of matrix, reservoir (conventional CR system), or osmotic systems. In matrix systems, the drug is embedded in a polymer matrix and the release takes place by partitioning of drug into the polymer matrix and the release medium. In contrast, reservoir systems have a drug core surrounded/ coated by a rate controlling membrane. However, some factors like pH, presence of food, and other physiological factors may affect drug release from conventional CR systems. Osmotic systems utilize the principles of osmotic pressure for the delivery of drugs. Drug release from these systems is independent of pH and other physiological parameters to a large extent and it is possible to modulate the release characteristics by optimizing the properties of drug and system [2]. Alza Corporation of the USA was first to develop an oral osmotic pump and today also, they are the leaders in this field with a technology named OROS™. The oral osmotic pumps have certainly come a long way and the available products based on this technology makes its presence felt in market [3]. They are also known with different name like GITS (gastro-intestinal therapeutic system), different types of osmotic pumps are available to meet variety of drug delivery demands (Table-1). Osmotic pumps can be used as experimental tools to determine important pharmacokinetic parameters of new or existing drugs. At the same time, they can also be utilized to deliver drugs at a controlled and predetermined rate [4]. In this review article, the formulation aspects that are important in the development of oral osmotic systems discuss.

MECHANISM OF OSMOSIS

Core contain water soluble osmotically active agent and blended with water soluble or insoluble drug, additives and coating has been carried out which functions as semi permeable membrane.

Since barrier is only permeable to water, initial penetration of water dissolves the critical part of the core, resulting in development of an osmotic pressure difference across the membrane.

The device delivers a saturated volume equal to the volume of water uptake through the membrane. Initial lag time (per hour) during which delivery rate increases to its maximum value, drug release is zero order, until all solid material is dissolved.

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

$$\Pi V = n_2 RT$$

Where, V = is the volume of solution
n_2 = is number of moles of solute
T = thermodynamic temperature
R = is the gas constant

PRINCIPLE OF OSMOSIS

The solvent membrane control delivery of agent from the osmotic system across the semi permeable membrane, which in turn drive the agent out. Water influx of osmotic pump can be describe as,

$$\frac{dv}{dt} = \frac{A}{h} LP\,\sigma\,(\Delta\Pi - \Delta P)$$

Where $\frac{dv}{dx}$ = Water influx,
A = Membrane area,
h = Membrane thickness,
P = Mechanical permeability,
ΔΠ = Osmotic pressure,

ΔP = Hydrostatic pressure difference between inside and outside the system

The general expression for the solute delivery rate, dM / dt obtained by pumping through the orifice of the reservoir is given by,

$$\frac{dM}{dt} = \frac{dV}{dt} C$$

Where C = Concentration of solute if dispersed fluid

σ describes the leakages of solute through the membrane.

A perfect semi permeable membrane is selectively permeable to water only and does not allow solute to pass through it (σ is close to unity). By substituting the product of LP σ with membrane permeability k, equation becomes,

$$\frac{dM}{dt} = \frac{A}{h} k\Pi C$$

It is possible to obtained constant zero order release rate from osmotic system by maintaining the terms on right side of equation constant. As long as the excess solid osmotic agent is present inside the system both Π and C can be maintained at constant level corresponding the saturated solution of agent.

Above equation describe to all osmotically driver system including EOP and the agent reservoir (Alzet osmotic pumps). Here drug release also described by equation combining osmosis and diffusion component.

The diffusion component is added because the membrane used is not perfectly semi permeable in nature and thus a portion of drug is released by diffusion permeability through the pores in the coating. The total mass delivery dM / dT per unit time is given by,

$$\left[\frac{dM}{dT}\right]_t = \left[\frac{dM}{dT}\right]_0 + \left[\frac{dM}{dT}\right]_d$$

Where mass released by pumping and diffusion respectively and osmotic release component is given by,

$$(dM / dT)_d = P_d A C / h$$

Where P_d = dissolved drug permeability.

The push pull osmotic pump consists of two compartments and is coated with a semi permeable membrane. Drug along the osmotic agent is present in upper compartment, whereas lower compartment consist of osmotic agent. The drug compartment is connecting to outside environment via delivery orifice. After coming in contact with aqueous environment, imbibitions of fluid by the drug compartment take place to form the fluid composition that is delivered by the delivery orifice. Simultaneously imbibition of fluid by the push compartment causes it to swell and co-operate with the drug composition for delivering the drug from delivery orifice.

The mass delivery from the push pull osmotic pump is given by,

$$dM / dT = (Q + F) F_d C_0$$

Where, Q and F are osmotic flow in the osmotic and drug compartment respectively

F_d is the fraction of drug formulated in drug compartment.

C_0 is the concentration of solid dispersion.

FACTORS AFFECTING RELEASE OF MEDICAMENT

1. Solubility
2. Osmotic pressure
3. Orifice Size
4. Membrane type
5.

1. Solubility

Solubility of drug is one of the most important factors since kinetic of osmotic release is directly related to the drug solubility.

The fraction of a drug release with zero order kinetic is given by

$$F(z) = 1 - S/P$$

Where F (z) = fraction release by zero order

S = drug solubility in g / cm^3

P = density of core tablet in g / cm^3.

Drug with density of unity and solubility <0.05 g / cm^3 would release ≥ 95 % by zero order kinetics. Drug with density ≥ 0.3 g / cm^3 solubility would demonstrate with higher release rate ≥ 70 % by zero order.

However, the zero order release rate would be slow, due to the small osmotic pressure gradient. Conversely, highly water-soluble drugs would demonstrate a high release rate that would be zero-order for a small percentage of the initial drug load. Thus, the intrinsic water solubility of many drugs might preclude them from incorporation into an osmotic pump. However, it is possible to modulate the solubility of drugs within the core, and thus, extend this technology for delivery of drugs that might otherwise have been poor candidates for osmotic delivery. Some of the approaches that have been used to deliver drugs having extremes of solubility are:

Sr No	Type of approches	Mechanism	Examples
1	Use pf Wicking agents [5]	Enhance the surface area of drug with the incoming aqueous fluids	Colloidal silicon dioxide, sodium lauryl sulfate, etc
2	Resin Modulation approach [6]	Ion-exchange resin methods are commonly used to modify the solubility of drugs	Poly (4-vinyl pyridine), Pentaerythritol, Citric and Adipic acids
3	Use of swellable polymers [7]	Polymers have uniform swelling rate which causes drug release at constant rate	Vinyl acetate copolymer, Polyethylene oxide
4	Use of effervescent mixtures [8]	Creates pressures in the osmotic system and ultimately controls the release rate	Mixture of Citric acid and Sodium bicarbonate
5	Use of cyclodextrin derivatives [9]	They are known to increase solubility of poorly soluble drugs.	---
6	Use of alternative salt form [10]	Change in salt form may change physico-chemical property of active ingredients.	In case of Oxprenolol, found that hydrochloride salt of Oxprenolol was too soluble to maintain a saturated solution and hence zero order delivery for the anticipated delivery life of dosage form. Subsequently succinate salt was found to have optimum solubility, and osmotic pump was formulated with this salt form that give extended release up to 24 h
7	Use of encapsulated excipients [11]	Solubility modifier excipients used in form of mini-tablet coated with rate controlling membrane	---
8	Use of crystal habit modifiers [12]	Different crystal form of the drug may have different solubility, so the excipients which may change crystal habit of the drug can be used to modulate solubility.	---

Sr No	Type of approches	Mechanism	Examples
9	Co-compression of drug with excipients [13]	Different excipients can be used to modulate the solubility of drugs with different mechanisms like saturation solubility, pH dependent solubility.	Organic acids, Buffering agent, etc.

2. Osmotic Pressure

To achieve a zero-order release rate, it is essential to keep constant osmotic pressure by maintaining a saturated solute solution. Many times, the osmotic pressure generated by the saturated drug solution may not be sufficient to achieve the required driving force. In this case, other osmotic agents are added that enhance osmotic pressure. For example, addition of bicarbonate salt not only provides the necessary osmotic gradient but also prevents clogging of the orifice by precipitated drug by producing an effervescent action in acidic media [14].

Rate of drug release from an Osmotic system is directly proportional to Osmotic Pressure of the core formulation

$$\frac{dM}{dt} = \frac{A\ k\ \Pi\ C}{h}$$

In order to achieve optimized and constant Osmotic Pressure in compartment Osmotic agent must be added to tablet. So varying the osmogents vary osmotic pressure and hence drug release.

3. Orifice Size

To achieve an optimal zero-order delivery profile, the cross sectional area of the orifice must be smaller than a maximum size S_{max} to minimum drug delivery by diffusion through orifice. Furthermore, the area must be sufficiently large, above a minimum size S_{min}, to minimize the hydrostatic pressure buildup in the system. Otherwise, the hydrostatic pressure can deform the membrane and affect the zero-order delivery rate. Therefore, the cross sectional area of the orifice S_o should be maintained between minimum and maximum values. Typically, a diameter of about 0.2 mm through a membrane thickness of 0.2 mm thickness is needed to maintain a delivery rate on the order of 10 mg/h for water soluble compounds [15]. The minimum cross sectional area can be estimated from the following equation:

$$S_{min} = 5\left[\left(\frac{L}{P_{max}}\right)\mu\left(\frac{dV}{dt}\right)\right]^{1/2}$$

Where, dV/dt = volume of flux through an orifice

L = length of the orifice (usually the same as thickness of the membrane)

μ = viscosity of the drug solution flowing through the orifice

P_{max} = maximum tolerated hydrostatic pressure difference across the membrane before occurrence of deformation of the housing

The maximum cross sectional area of the orifice is obtained by specifying that the release rate must be smaller than a fraction f of the zero order pumping rates and is defined by following equation:

$$S_{max} = \frac{M_{tz} f L}{D_s C_s}$$

Where M_{tz} = the amount of the drug delivered in zero order fashion,

D_s = drug diffusion coefficient in the permeating solvent.

4. Membrane Type

Semipermeable membrane is permeable to water and not to ions, the release rate is essentially independent of the pH of the environment. The drug dissolution process takes place inside the delivery system, completely separated from the environment [10].

Formulation of Osmotic Drug Delivery System

Core Composition	Coating Composition
• Active Drug	• Polymer
• Filler	• Plasticizer
• Viscosity modifier	• Membrane modifier
• Solubilizer	• Color and Opacifier
• Lubricant or Glidant	

A) Drug

Drug itself may act as an osmogen and shows good aqueous solubility (e.g., Potassium chloride pumps). But if the drug does not possess an osmogenic property, osmogenic salt and other sugars can be incorporated in the formulation[16-18].

B) Semi-Permeable Membrane

Semipermeable membrane must possess certain performance criteria:

- ✓ It must have sufficient wet strength and water permeability.
- ✓ It should be selectively permeable to water and biocompatible.

The unique feature of Semipermeable membrane utilized for an osmotic pump is that it permits only the passage of water into the unit, thereby effectively isolating the dissolution process from the gut environment.

Some other polymers such as Agar acetate, Amylose triacetate, Betaglucan acetate, Poly (vinylmethyl) ether copolymers, Poly (orthoesters), Poly acetals, Poly (glycolic acid) and Poly (lactic acid) derivatives.

C) Osmogen / Osmagent / Osmotic Driving Agent

Osmotic agents are classified as,

a) Inorganic water soluble osmogen: Magnesium sulphate, Sodium chloride, Sodium sulphate, Potassium chloride, Sodium bicarbonate, etc.
b) Organic polymeric osmogens: Na CMC, HPMC, HEMC, etc.
c) Organic water soluble osmogen: Sorbitol, Mannitol, etc

D) Hydrophilic and Hydrobhobic Polymers

These polymers are used in the formulation development of osmotic systems containing matrix core. The selection of polymer is based on the solubility of drug as well as the amount and rate of drug to be released from the pump.

The highly water soluble compounds can be co-entrapped in hydrophobic matrices and moderately water soluble compounds can be co-entrapped in hydrophilic matrices to obtain more controlled release.

Hydrophilic Polymers: Hydroxy Ethyl Cellulose, Carboxy Methyl Cellulose, Hydroxyl Propyl Methyl Cellulose, etc.

Hydrophobic Polymers: Ethyl Cellulose, Wax materials, etc.

E) Surfactants

They are added to wall forming agents. They act by regulating the surface energy of materials to improve their blending in to the composite and maintain their integrity in the environment of use during the drug release period.

Examples: Polyoxyethylenated glyceryl recinoleate, Polyoxyethylenated castor oil having Ethylene oxide, Glyceryllaurates, etc.

F) Coating Solvents

Solvents suitable for making polymeric solution that is used for manufacturing the wall of the osmotic device include inert inorganic and organic solvents[19].

Examples: Methylene chloride, Acetone, Methanol, Ethanol, Isopropyl alcohol, Ethyl acetate, Cyclohexane, etc.

G) Plasticizers

Permeability of membranes can be increased by adding plasticizer, which increases the water diffusion coefficient[20].

Examples: Dialkyl phthalates, Trioctyl phosphates, Alkyl adipates, Triethyl citrate and other Citrates, Propionates, Glycolates, Glycerolates, Myristates, Benzoates, Sulphonamides and Halogenated phenyls.

H) Flux Regulators

Flux regulating agents or flux enhancing agent or flux decreasing agent are added to the wall forming material; it assist in regulating the fluid permeability through membrane.

Examples: Poly hydric alcohols such as Poly Alkylene Glycols and low molecular weight glycols such as Poly Propylene, Poly Butylene and Poly Amylene, etc.

I) Pore Forming Agents

These agents are particularly used in the pumps developed for poorly water soluble drug and in the development of controlled porosity or multi particulate osmotic pumps.

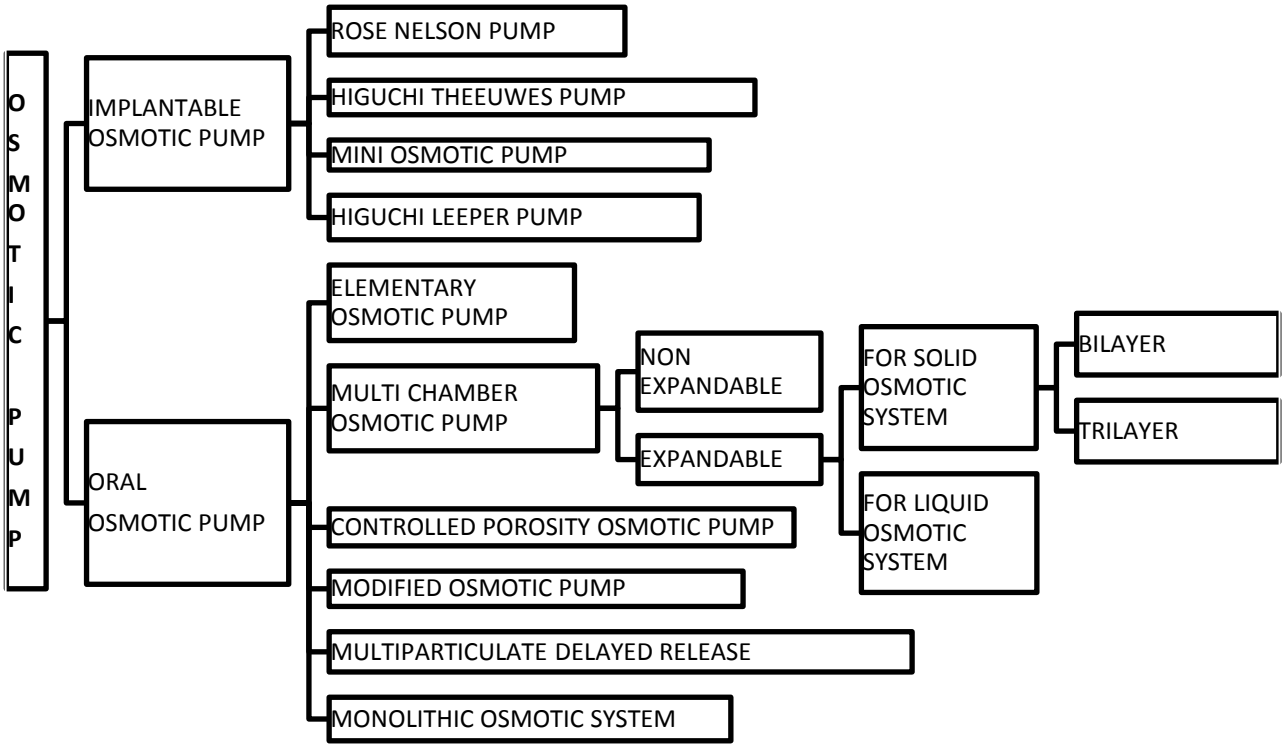
The pore formers can be inorganic or organic and solid or liquid in nature. Like,

→ **Alkaline Metal** salts such as Sodium chloride, Sodium bromide, Potassium chloride, etc.

→ **Alkaline earth metals** such as Calcium chloride and Calcium nitrate

→ **Carbohydrates** such as Glucose, Fructose, Mannose, etc.

Osmotic Drug Delivery Devices:



A. Implantable Osmotic Pumps:

Sr. No	Type of dosage form	Mechanism of drug release	Composition
1.	Rose Nelson Pump	Due to difference in osmotic pressure across membrane, water moves from water chamber into the salt chamber. As a result, volume of the salt chamber increases because of this water flow which distends the diaphragm separating the salt & drug chambers, thereby pumping drug out of the device.	• A drug chamber with orifice • A salt chamber containing solid salt and elastic diaphragm • A water chamber
2.	Higuchi-Leeper Pump: (Simplified version of Rose-Nelson pump)	The pump is activated when it is swallowed or implanted in the body. This pump consists of a rigid housing, and the semipermeable membrane is supported on a perforated frame. It has a salt chamber containing a fluid solution with excess solid salt. Recent modification: pulsatile drug delivery, achieved	• Rigid housing, divided in two chambers by a movable separator • Semi permeable membrane, which is supported on a perforated frame.

Sr. No	Type of dosage form	Mechanism of drug release	Composition
		by the production of a critical pressure at which the delivery orifice opens and releases the drug.	
3.	Higuchi-Theeuwes Pump	The device is loaded with drug prior to use. Semi permeable wall acts as a rigid outer casing of the pump. Release of drug depends on time course set by the salt used in the salt chamber and the permeability of the outer membrane casing.	• A salt chamber • Semi permeable membrane
4.	Implantable Mini Osmotic Pump (Oralzet Osmotic Pump)	Most advanced version of implantable pumps Water enters the sleeve through semi permeable membrane when the system comes in contact with aqueous environment, compresses the flexible drug reservoir and displaces the drug solution through the flow moderator. Delivery rates & delivery duration can be modified between 0.25 to 10 ml/hour and between 1 day and 4 weeks simultaneously.	Composed of three concentric layers – • Drug reservoir – inner most compartment • Osmotic sleeve - a cylinder containing high concentration of osmotic agent • Rate controlling semi permeable membrane. • Additional component, flow moderator, is inserted into the body of the osmotic pump after filling.
5.	DUROS® Osmotic Pump	Based on osmosis principle, releases of therapeutic agent can be achieved at a predetermined rate. Extracellular fluid enters in to the device through a semipermeable membrane directly into a salt engine which expands to drive the piston at a slow and even delivery rate. Piston movement forces the drug formulation to be released through the orifice or exit port.	DUROS® (applied to human parenteral therapy) technology shaped as a small rod with titanium housing. It consists of sterile, non biodegradable, single-use devices for continuous, subcutaneous administration of therapeutic molecules at steady rates. Therapeutic molecules can deliver for durations ranging from 3 to 12 months by this technology.

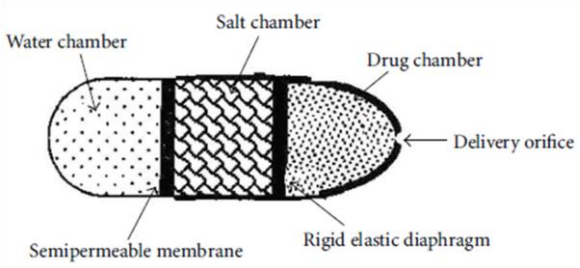


Fig 1: Rose Nelson Pump

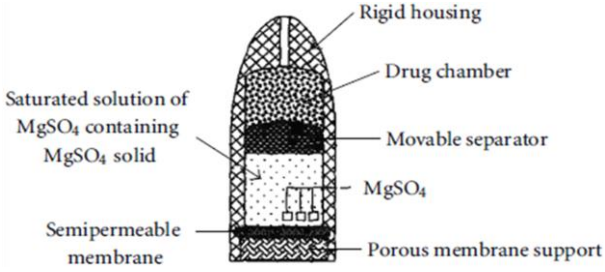


Fig 2: Higuchi-Leeper Osmotic Pump

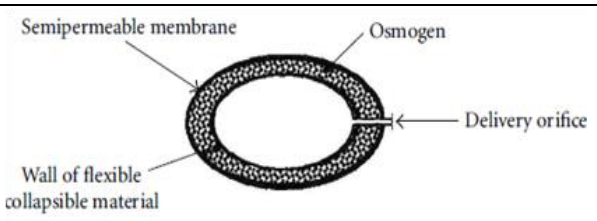


Fig 3: Higuchi Theeuwes Pump

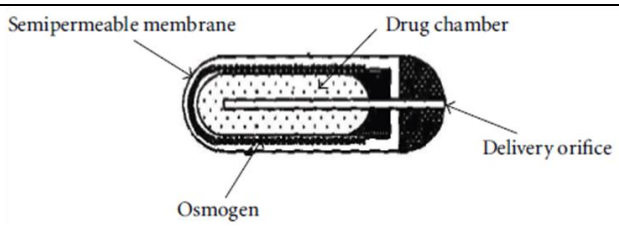


Fig 4: Alzet Pump

B. Oral Osmotic Pumps:

As oral route is the most popular route of administration, most of the osmotic systems are developed as oral drug delivery. It is possible to deliver drugs at zero-order release rate, independent of gastric pH and hydrodynamic conditions with these osmotically controlled drug delivery systems.

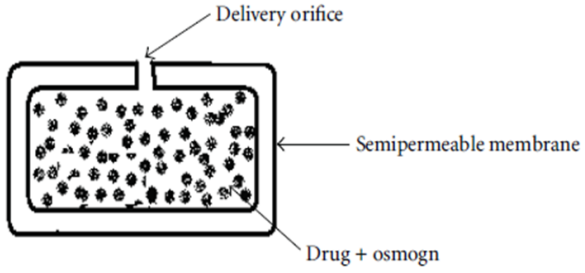
These systems can be further classified in

a) Single chamber osmotic system: Elementary osmotic pump
b) Multi-chamber osmotic systems:
   a. Tablets with second expandable osmotic chamber: push-pull osmotic pump
   b. Tablets with second non-expandable osmotic chamber:
      i. Two systems fall in this class i.e.
         1. Drug solution gets diluted in the second chamber before leaving device and
         2. Two separate EOP tablet formed in a single tablet
   c. Miscellaneous:
      i. Controlled porosity osmotic pumps,
      ii. Multi particulate osmotic pump,
      iii. Osmotic bursting osmotic pump,
      iv. Effervescent activity-based osmotic systems,
      v. Lipid osmotic pump.

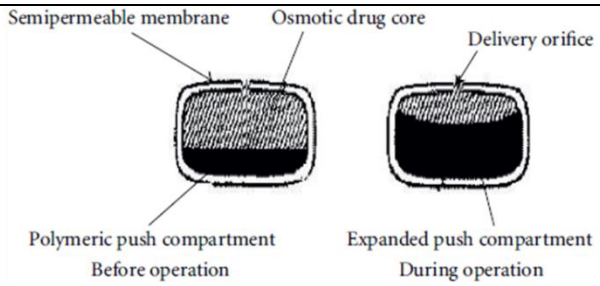
Sr No	Type of dosage form	Mechanism of drug release	Composition
1.	Elementary Osmotic Pump: (Combination of Effervescent Agents with the Drug)	When comes in contact with water, water penetrates inside the dosage form by the fluid permeability of the membrane and osmotic pressure of core formulation at the determined rate. So the saturated solution of drug occurs within the core, which is dispensed at a controlled rate from the delivery orifice available on membrane.	• Osmotic core containing drug (may or may not contain osmogent depending on osmotic activity of drug), • Semipermeable membrane (usually of cellulose acetate), • Delivery orifice
2.	Push-Pull Osmotic Pump: (Modified EOP)	Osmotic agents attract water into both the layers of tablet when the system comes in contact with aqueous environment. As a result, drug layer pulls water into the compartment to form in situ a suspension of drug, and simultaneously non-drug layer attract water into that compartment to expand volumetrically and pushes the drug suspension out of the delivery orifice.	A standard coated bilayer tablet. • One layer (upper layer): drug, polymeric osmotic agent (ability to form a suspension of drug in situ) and other tablet excipients. • The other layer contains: Osmotic and coloring agents, Polymer and tablet excipients. These layers are formed and bonded together by

Sr No	Type of dosage form	Mechanism of drug release	Composition
			compression to form a single bilayer core. • Coated with semipermeable membrane. • After the coating has been applied, a small hole is drilled.
3.	Osmotic Bursting Osmotic Pump:	When comes in contact with an aqueous environment, water is imbibed which built up hydraulic pressure inside until the wall rupture and release the contents to the environment.	• This system is similar to an EOP except delivery orifice is absent and size may be smaller
4.	Controlled Porosity Osmotic Pump (CPOP):	Low levels of water-soluble additive are leached from polymer materials that were permeable to water yet remained insoluble, when exposed to water, and forms sponge like structure with controlled porosity walls permeable to both water and dissolved drug agents.	Single or multi-compartment dosage form • Core with the drug surrounded by a membrane which has an asymmetric structure • Semi Permeable Membrane • Pore forming additive dispersed throughout the wall.
5.	Osmotic pumps for insoluble drugs:	With the contact of water, osmotic agent swells inside the membrane & delivers drug delivers insoluble drug out of orifice through hydrostatic force.	• Drug mix with pre-coated particles of osmotic agents particles with an elastic semipermeable membrane. • Coated with rigid semipermeable membrane.
6.	Sandwiched Osmotic Tablets (SOTS):	The middle push layer containing the swelling agents swells when comes in contact with aqueous environment. Due to this, drug is released from the two orifices situated on opposite sides of the tablet and thus SOTS can be suitable for drugs prone to cause local irritation of the gastric mucosa.	• Polymeric push layer sandwiched between two drug layers with two delivery orifices.
7.	Monolithic Osmotic System:	Polymer matrix capsule surrounding the drug ruptured due to water imbibitions by active agents; so start to release it to the outside environment, when the system comes in contact with the aqueous environment.	• It constitutes a simple dispersion of water-soluble agent in polymer matrix.
8	Pelleted delayed release:	Expansion of membrane takes place due to system come in contact with water, which causes pore formation and as a result drug release from system. This system is suitable for higher release rate for poorly water soluble drugs because of high flux rate.	• Pellets of drug, with or without osmogents • Coated with semipermaeble membrane.
9	Liquid oral osmotic system (L-Oros):	Osmotic layer activates when water permeates across the rate controlling membrane. So the hydrostatic pressure builds up inside the system due to expansion of the osmotic layer and forces the liquid formulation to break through the hydrated gelatin capsule shell at the delivery orifice. Suitable for controlled delivery of lipophilic drugs.	• Liq. Drug formulation is present in a soft gelatin capsule surrounded with • Barrier layer, • Osmotic layer (release rate controlling membrane) • A delivery orifice is formed through these layers.
10	OROS-CT (colon	Enteric coating prevents entry of fluids from	Used as a once or twice a day

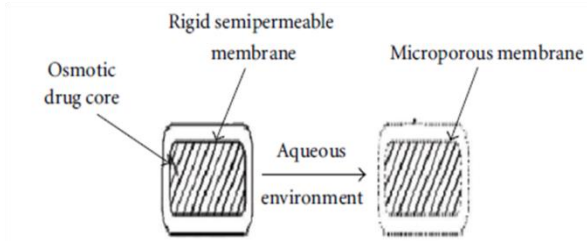
Sr No	Type of dosage form	Mechanism of drug release	Composition
	targeting):	stomach to the system when gelatin capsule dissolves with contact to water. Enteric coating dissolves when the system enters into the small intestine and water penetrates into the core, so the push compartment to swell. Simultaneously, flowable gel is formed in the drug compartment and pushed out of the orifice by the rate of water transport across the semi permeable membrane.	formulation for targeted delivery of drugs to the colon. The OROS-CT can be a single osmotic agent or it can comprise of as many as five to six push pull osmotic unit filled in a hard gelatin capsule.



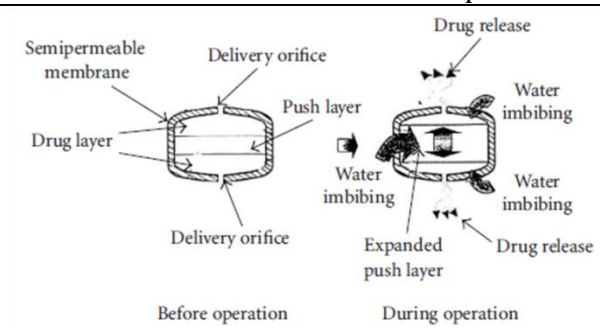
Elementary Osmotic Pump



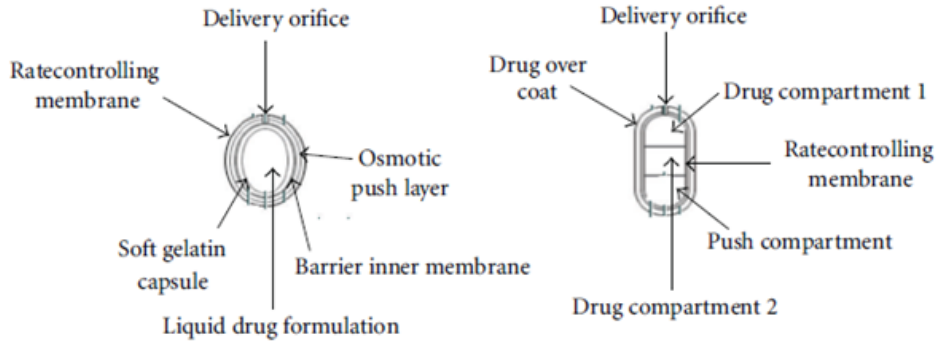
The Push-Pull Osmotic Pump



Controlled Porosity Osmotic Pump (CPOP)



Sandwiched Osmotic Pump



Liquid oral Osmotic Pump

In Vitro Evaluation:

1. **In-vitro Dissolution:**

The in vitro release of drug from oral osmotic system has been evaluated by the conventional USP paddle and basket type apparatus. Temperature of dissolution media was kept at 37 ± 0.5 ºC. The dissolution media is generally **distilled water** as well as **stimulated gastric fluid (for first 2-4 hr)** and **stimulated intestinal fluids (for subsequent hours)** have been used. The samples were withdrawn (10ml) at different time intervals and replaced with 10 ml of fresh media. The standard specification, which are followed for the oral controlled drug

delivery systems are equivalently applied for oral osmotic pump. Samples were analyzed using UV spectrometer[16].

2. **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. Membranes were dried at 45 °C for 12 h and stored between sheets of wax paper in a dessicator until examination [17].
3. **Effect of pH:**
   To study the effect of pH on drug release, in vitro release studies can be conducted in dissolution media having different pH to assure a reliable performance of the developed formulations independent of pH. Dissolution was carried in 900 ml of 0.1 N HCl, pH 4.5 acetate buffer and pH 6.8 phosphate buffer, pH 7.5 phosphate buffer and distilled water. Dissolution apparatus (USP-II) was used for drug release study. The samples (10ml) were withdrawn at predetermined intervals and analyzed using UV spectrometer.
4. **Effect of Agitational Intensity:**
   To study the effect of agitation intensity on drug release, optimized formulation was subjected to dissolution at various rotation speeds. Dissolution was carried out in USP-II (Paddle) at various rotational speeds like 50, 100 and 150 rpm. The samples (10ml) were withdrawn at predetermined intervals and analyzed using UV spectrometer and compared [18].
5. **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 for confirming the mechanism of drug release.. To increase the osmotic pressure of the release media (pre-equilibrated to 37°C ± 1°C), osmotically effective solute (mannitol, sodium chloride etc.) with different concentration can be added. 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. The osmotic pressure of the medium was determined using Van't Hoff and Morse equation[18].

$$\pi V = nRT$$

Where, π – Osmotic pressure,
V- Volume of the solution in liter,
n-Number of moles of solute,
T- Absolute temperature,
R- Gas constant (0.082 lit atm/mol deg.)

OPTIMIZATION:

In the numerical optimization techniques, the desirability approach was used to generate the optimum settings for the formulation. For the optimized formulation, the drug release at 2 h, 4 h, 8 h, 12 h, T50%, release exponent(n) were kept in target. The drug release target was kept according to the USP standards.

A. Powder flow properties

a) Angle of repose

The angle of repose of the mixture of the drug and excipients was determined by fixed funnel method. The values are used in the following equation to get the angle of repose.

$$\tan \theta = h/r$$

Where, h, r and θ are the height, radius and angle of repose of the powder pile.

b) Bulk density

Accurately weighed 3 g of the sample was transferred to the measuring cylinder of bulk density apparatus. The apparatus was adjusted for 100 tapping and noted the final volume as tapped volume.

$$\text{Tapped density } (\rho t) = \frac{\text{Weight of the powder}}{\text{Tapped volume of the powder}}$$

c) Porosity

Porosity of the powder was determined by using formula:

$$\text{Porosity} = [(V_b - V_p)/ V_b] \times 100.$$

Where V_b and V_p = bulk volume and true volume respectively.

d) Carr's index[19]

The carr's index of the powder was determined by using formula:

$$Carr's\ index(\%) = \frac{(TBD - LBD)}{TBD} \times 100$$

Where, TBD = total bulk density and
LBD = loose bulk density

B. Evaluation of Porous osmotic pump Tablets

a. Thickness

Thickness of the core tablets and coated tablets were measured by using screw gauge. Ten tablets from each formulation were randomly selected and used. Thickness is expressed in millimeters.

b. Hardness

The hardness of the core tablets and coated tables were measured using the hardness tester. Six tablets from each formulation were randomly selected and used. The average hardness and the standard deviation were calculated.

c. Friability

Friability of the matrix tablets and core tablets of porous osmotic pump tablets were determined. 10 tablets were randomly selected, weighed and placed in the friabilator. The apparatus was rotated at 25 rpm for 4 min. After revolutions the tablets were dedusted and weighed again. The percentage friability was measured using the formula

$$\%\ \text{Friability} = \frac{\text{Initial wt of tablets} - \text{Final wt of tablets}}{\text{Initial wt of tablets}} \times 100$$

d. Weight uniformity

Ten tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated[19].

e. Determination of drug content

Ten tablets were accurately weighed and powdered. The standard specification, which are followed for the oral controlled drug delivery systems are equivalently applied for oral osmotic pump. A sample can be analyzed spectrophotometrically at relevant wavelength. Amount of drug present was determined from the calibration curve [20].

f. Curve fitting Analysis [21-23]

For the determination of the drug release kinetics from the porous osmotic pump tablet, the *in vitro* release data were analyzed by zero order, first order, Higuchi and Korsmeyer and Peppas equations.

i. Zero order release kinetic

To study the zero order release kinetics the release data was fitted into the following equation:

$$dQ/dt = K_0$$

Where, Q = amount of drug release,
K_0= zero order release rate constant and
t = release time.

The graph is plotted percentage cumulative drug release (% CDR) verse time.

ii. First order release kinetic

To study the first order release kinetics the release rate data are fitted into the following equation:

$$dQ/dt = K_1 Q$$

Where, Q= fraction of drug release,
K_1= first order release rate constant
t= release time.

The graph is plotted log % CDR remaining verse time.

iii. Higuchi release model

To study the Higuchi release model the release rate data are fitted into the following equation:

$$Q = K_H t^{½}$$

Where, Q = fraction of drug release,
K_H= release rate constant and
t = release time.

The graph is plotted % CDR verses square root of time.

iv. Korsmeyer and Peppas kinetics

To study the Korsmeyer and Peppas release kinetics the release rate data are fitted in to following equation:

$$Mt/M\infty = K_{KP}t^n$$

Where, $Mt/M\infty$ = the fraction of drug release,

K_{KP} = release rate constant

t = release time and

n = diffusion exponent related to mechanism of drug release.

The graph is plotted log %CDR verses log time

g. Stability

The purpose of stability study is to provide evidence on the quality of a drug substance or drug product which varies with time under the influence of a variety of environmental factors such as temperature, humidity and light. The formulation was subjected to accelerated stability studies as per ICH (The International Conference of Harmonization) guidelines. The most satisfactory formulation was sealed in an aluminum foil and stored at 30 ± 2ºC, 65 ± 5% RH and at 40 ± 2 ºC, 75 ± 5% RH for 6 months. Tablets were periodically removed and evaluated for physical characteristics, in-vitro drug release [24].

REFERENCES:

1. R.K. Verma, S. Garg, Current status of drug delivery technologies and future directions, Pharm. Technol.-On Line (http: / /www.pharmaportal.com) 25 (2001) 1–14.
2. F. Theeuwes, D.R. Swanson, G. Guittard, A. Ayer, S. Khanna, Osmotic delivery systems for the beta-adrenoceptor antagonists metoprolol and oxprenolol: design and evaluation delivery, J. Control. Release 35 (1995) 127–136. , Br. J. Clin. Pharmacol. 19 (1985) 69S–76S.
3. Santus G, Baker, RW. Osmotic drug delivery: A review of the patent literature, J. Control. Release 35 (1995)
4. Verma RK, Mishra B, Garg S, Osmotically controlled oral drug delivery, Drug Dev. Ind. Pharm. 26 (2000) 695–708.
5. Gohel MC, Parikh RK, Shah NY. Osmotic Drug Delivery – An Update. Pharmaceutical Reviews 2009; 7 (2). Available at www.pharmainfo.net
6. Zentner GM, McClelland GA, Sutton SC. Controlled porosity solubility and resin modulated osmotic drug delivery systems for release of diltiazem hydrochloride. J Control Release 1991; 16(1-2): 237-244.
7. Khanna SC, Inventor; Ciba-Geigy Corporation, Ardsley, NY, Assignee. Therapeutic system for sparingly soluble active ingredients. US patent 4 992 278. 1999 Feb 12.
8. Theeuwes F, Inventor; ALZA Corporation, Palo Alto, CA, Assignee. Osmotic dispenser with gas generating means. US patent 4036 228.1977 Jul 19.
9. Okimoto K, Miyake M, Ohnishi N, et al. Design and evaluation of an osmotic pump tablet for prednisolone using (SBE)-7m-s-CD. Pharm Res 1998; 15: 1562-1568.
10. Theeuwes F, Swanson DR, Guittard G, et al. Osmotic delivery systems for the beta adrenoceptor antagonists metoprolol and oxprenolol: Design and evaluation of systems for once-daily administration. Br J Clin Pharmacol 1985; 19 (suppl 2):69S–76S.
11. Bauer K., Kaik G. and Kaik B. (1994). Osmotic release oral drug delivery system of metoprolol in hypertensive asthmatic patients. Pharmacodynamic effects on beta 2-adrenergic receptors, Hypertension, 24:339-346.
12. Rudnic E.M., Burnside B.A., Flanner H.H., Wassink S.E., Couch R.A. and Pinkett J.E. (2000). Osmotic drug delivery system. US Patent 6110498.
13. Thombre A.G., DeNoto A.R. and Gibbes D.G. (1999). Delivery of glipizide from asymmetric membrane capsules using encapsulated excipients. J. Control. Release, 60, 333-341.
14. Cole, Hogan and Aulton (2003). Pharmaceutical Coating Technology Modified Release Coating, 413-414.
15. Thombre AG, De Noto AR, Gibbes DG. Delivery of glipizide from asymmetric membrane capsules using encapsulated excipients. J Control Release 1999; 60: 333-341.
16. Koparkar AD, Shah SB, Inventors; Ciba-Geigy Corporation, Ardsley, NY, Assignee. Oral osmotic system for slightly soluble active agents. US patent 5 284 662. 1994 Feb 8.
17. Swanson D, Edgren D, Inventors; ALZA Corporation, Palo Alto, CA, Assignee. Osmotic device that improves delivery properties of agent in situ. US patent 4326525. 1982 Apr 27.
18. Santus G, Baker RW. Osmotic drug delivery: A review of the patent literature. J Control Release 1995; 35(1):1–21.

19. Good WR, Lee PI. Membrane-controlled reservoir drug delivery systems. In: Langer RS, Wise DL. Medical Applications of Controlled Release. Vol 1, Boca Raton: CRC Press; 1984. 1–39.
20. Makhija SN, Vavia PR. Controlled porosity osmotic pump-based controlled release systems of pseudoephedrine I. Cellulose acetate as a semi permeable membrane. J Control Release 2003; 89:5-18.
21. Prakash RB, Geetha M, Purushothama N, Utpal S. Optimization and development of swellable controlled porosity osmotic pump tablet for theophylline. Trop J Pharm Research 2009; 8(3):247-55.
22. Kanagale P, Lohray BB, Misra A, Davadra P, Kini R. Formulation and optimization of porous osmotic pumpbased controlled release system of oxybutynin. AAPS Pharm Sci Tech 2007; 8(3):E1-E7.
23. Ayhan S, Yalcin O, Askin I, Imer. Preparation and in vitro evaluation of sustained release tablet formulations ofdiclofenac sodium. Farmaco 2005; 60:171-77.
24. Donald LW. Hand book of Pharmaceutical Controlled Release Technology. New York: Marcel Dekker; 2000, p.183-88, 225-54, 431-36.