

## Controlled Porosity Osmotic Pump Drug Delivery: A Review on Its Use in Hypertension and Beta Blocker Therapy

Müller, Klaus Peter<sup>1</sup> & Schmidt, Anna Maria<sup>2</sup>

<sup>1</sup>Department of Mechanical Engineering, Technical University of Munich, Germany

<sup>2</sup>Institute of Advanced Materials, University of Berlin, Germany

### **Abstract**

**Keywords:** *Beta blockers, Colligative property, Cardiac output, Hypertension, Osmosis.*

A significant milestone in oral NDDS is osmotic drug delivery system. Osmotic system releases a drug at a predetermined zero order delivery rate based on osmosis. The osmotic pressure is a colligative property of a solution in which the magnitude of osmotic pressure of the solution is independent on the number of discrete entities of solute present in the solution. The release rate depends on solubility, molecular weight and activity coefficient of the solute i.e osmogens. Elevated BP is an extremely common disorder affecting millions of people world wide. In most cases rise in B.P is due to increase in total peripheral resistance while cardiac output and heart rate are not high. The beta blockers are used individually or a combination therapy to treat hypertension. The development of oral osmotic systems has a strong and good market potential and it is clear from the marketed products and number of patents granted in the last few years. Beta blockers continue to be first choice drugs recommended by JNC VI & WHO-ISH. Hypertension is termed as ‘Silent killer’ as its symptoms are invisible many times, long term hypertension causes atherosclerosis, strokes, aneurysm, retinopathy in eyes and amputation of the parts. At this time focus was on developing zero order delivery system. Zero order kinetics would be superior as they maintain steady drug concentration in blood in treating hypertension effectively.

### **Introduction**

The new technologies have revolutionized the delivery of medication and provide many benefits, one of them is controlled drug delivery system it used in the long term therapy for treatment of chronic conditions like hypertension and heart diseases. Conventional formulations have many limitations, control release formulations are preferred to maintain uniform dosing, reduce dose and increase safety margins for high potency drugs. Hypertension is a chronic disease in which the blood pressure in the arteries is increased. It is expressed by two measurements i.e. systolic and diastolic pressures which are maximum and minimum pressures respectively. Sustained hypertension over time is a major risk factor for heart diseases, strokes and chronic kidney disease. Hypertension is caused when BP is above 180 systolic or above 110 diastolic. It is also a common cause of cardiovascular disorder and is generally associated with abnormal lipid and altered glucose metabolism thus managing of cardiovascular disease in particular becomes important to improve health of the patients.

As per American heart association (AHA) following ranges of blood pressure (BP) in (mm Hg):

- i. Normal BP is below 120 systolic and below 80 diastolic.
- ii. Pre hypertension is 120-139 systolic or 80-89 diastolic.
- iii. Stage 1 high BP (hypertension) is 140-159 systolic or 90-99 diastolic.
- iv. Stage 2 high BP (hypertension) is 160 or higher systolic or 100 or higher diastolic.

The Alza Corporation of USA was the first to develop oral osmotic pumps. The newer technologies developed recently in ODDS includes Ensotrol technology, Portab system developed by Andrx pharmaceuticals, Zeros tablet Technology by ADD drug delivery technologies based in switzerland, *The Port system* by Therapeutic system research laboratory Ann Arbor in USA, and also Durin technology which successfully released the drug up to 6 months in vivo by zero order drug release. In order to enhance the complete release of the drug volume amplifier delivery devices are used. In addition to drug and osmogens the volume amplifier is in the device. Amplifier increases the volume by generating gas and fills the compartment to release the drug. The osmotic pumps can be used as experimental tools to determine pharmacokinetic parameters of new and existing drugs.

- Conforming with JNC VI (1997), the WHO-ISH guidelines have graded BP (mmHg) and hypertension as:

*Table 1: Categories of hypertension and its ranges*

CATEGORY	SYSTOLIC	DIASTOLIC
Optimal	<120	<80
Normal	<130	<85
High normal	130-139	85-89
<b>Hypertension:</b>		
Grade I(Mild)	140-159	90-99
Grade II(Moderate)	160-179	100-109
Grade III(Severe)	≥180	≥110
Isolated systolic (ISH)	≥140	<90

*Table 2: Suitability of beta blockers*

S. no	Beta adrenergic blockers suitable for:
1	Angina or post MI patients
2	Coexisting anxiety or Tachycardia
3	Tense young patient
4.	Non obese, high renin hypertensive
5.	Low cost therapy
6.	Pregnancy (cardioselective and beta blockers with ISA)

According to first comprehensive high BP guidelines of US in 2017, stated high BP should be treated earlier when it reaches 130/80 mm Hg rather than 140/90. This was as per the new guidelines issued this year. High blood pressure is now defined as readings of 130 mm Hg and higher for the systolic BP measurements or readings of 80 and higher for diastolic measurement. This new guidelines stress the importance of using proper technique to measure BP. High BP accounts for the second largest number of diseases and stroke deaths. This was published by the American Heart Association and the American College of Cardiology for Detection, Prevention, Management and Treatment of high BP.

### **Mechanism for controlling blood pressure**

Arterial blood pressure is regulated within a narrow range to provide adequate perfusion of the tissues without causing damage to the vascular system, particularly the arterial intima. Arterial blood pressure is directly proportional to the product of the cardiac output and peripheral vascular resistance. In both normal and hypertensive individuals cardiac output and peripheral resistance are controlled mainly by two overlapping control mechanism, the baroreflexes mediated by the sympathetic nervous system, and the rennin - angiotensin-aldosterone system. Most antihypertensive drugs lower blood pressure by reducing cardiac output and or decreasing peripheral resistance.

#### **1. Baroreceptors and the sympathetic nervous system:**

Baroreflexes involving the sympathetic nervous system are responsible for the rapid moment - to - moment regulation of blood pressure. A fall in BP causes pressure-sensitive neurons (baroreceptors in the aortic arch and carotid sinuses) to send fewer impulses to cardiovascular centers in the spinal cord. This prompts a reflex response of increased sympathetic and decreased para sympathetic output to the heart and vascular, resulting in vasoconstriction and increased cardiac output.

#### **2. Renin - Angiotensin - Aldosterone system:**

The kidney provides the long term control of BP by altering the blood volume. Baroreceptors in the kidney respond to reduced arterial pressure (and to sympathetic stimulation of beta- adrenoceptors) by releasing the enzyme renin. This peptidase converts Angiotensinogen to Angiotensin I, Which is in turn converted to Angiotensin II in the presence of Angiotensin Converting Enzyme (ACE). Angiotensin II is the body's most potent circulating vasoconstrictor, causing an increase in BP. Angiotensin II stimulates aldosterone secretion, leading to increased renal sodium reabsorption and an increase in blood volume which contributes to further increase in BP.

### Actions of beta blockers

The beta blockers reduce blood pressure primarily by decreasing cardiac output. They may also decrease sympathetic outflow from the CNS and inhibit the release of renin from the kidneys, thus decreasing the formation of angiotensin II and secretion of aldosterone. The prototype beta blocker is Propranolol which acts at both beta 1 and beta 2 receptors. Newer agents such as Atenolol and Metoprolol are selective for beta 1 receptors. These agents are commonly used in disease states such as asthma, in which propranolol is contradicted due to its beta 2 mediated bronchoconstriction. Atenolol decreases the heart beat, which slows down with less force, reducing the amount of blood pumped through arteries which slows down the BP. It blocks the effects of adrenaline.

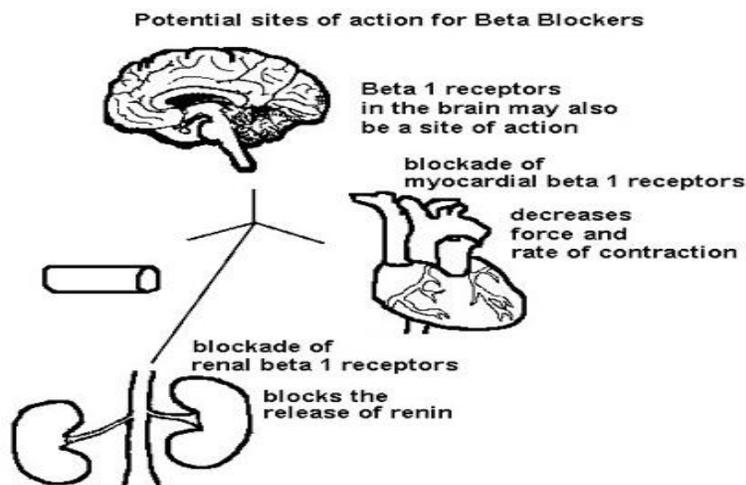


Figure 1: Sites of action of beta blockers

### Advantages & disadvantages of osmotic drug delivery system

#### Advantages:

1. Osmotic system is independent of pH and other physiological factors.
2. It reduces the rate of rise of drug concentration in blood.
3. They give sustained and consistence blood levels within the therapeutic window.
4. It gives enhanced bioavailability.
5. It helps in decreasing dose frequency.
6. Improves patient compliance and easy to formulate.
7. It shows customized delivery profiles.
8. They decrease the side effects.
9. They show good in-vitro and in vivo correlation (IVIVC).
10. The release is minimally affected by presence of food in GIT.
11. The release is highly predictable, they give zero order release profile after an initial lag. Zero order kinetics have better control over the drugs in vivo performance.
12. The release mechanisms are not dependent on drug.
13. Delivery rate is independent of agitation outside including GI motility.
14. Delivery of drug takes place in solution form ready for absorption with osmotic tablets simulating as a liquid dosage form prepared in-situ.
15. Drugs with widely varying solubility can be incorporated.

#### Disadvantages

1. If the coating is not even it causes film defects resulting in dose dumping.
2. Retrieval of drug is not possible in unexpected adverse effects.
3. It is expensive if the drilling is involved.
4. In other osmotic drug delivery systems size hole is critical
5. The drug integrity and consistency is difficult to maintain.
6. Inert ingredients are necessary for osmotic tablet formulations.

7. Special equipments are necessary for drilling orifices except for controlled porosity osmotic pumps.
8. Rapid development of tolerance is seen.
9. The osmotic tablets cannot be crushed or chewed.

#### **Osmosis principle:**

Osmosis depends on the chemical potential of solvent molecules in solution which is less than that of pure solvent. The solvent molecules spontaneously pass into the solution until the chemical potential of solvent and solution are equal. Pfeffer showed osmotic pressure ( $\Pi$ ) of the sugar solution is directly proportional to the solution concentration and the absolute temperature, later Vant hoff showed analogy. The osmotic pressure can be known from Vont hoff's equation:

$$\Pi = \phi CRT$$

$\phi$ = Osmotic coefficient of the solution

$\Pi$ =Osmotic pressure of solution

C=Molar concentration of the solute in the solution

R=Gas constant

T=Absolute Temperature

In terms of osmotic drug delivery system water is imbibed into the core osmotically through SPM resulting in development of hydrostatic pressure that pumps drug containing solution or suspension out of the core through one or more delivery ports. The delivery from the system is controlled by the water influx through SPM. Water influx into osmotic system can be described by the following:

$$dv / dt = A/h Lp (\sigma \Delta\Pi - \Delta P)$$

dv / dt=water influx

A=Membrane area

Lp = Mechanical permeability

$\sigma$  = Reflection coefficient

$\Delta\Pi$  and  $\Delta P$  Osmotic and Hydrostatic pressure differences between inside and outside of system

h= Thickness of membrane.

The best possible way to achieve a constant release from the osmotic systems is through proper selection and optimization of the semi permeable membrane.

#### **Literature review – patents**

1. Haisong Jiang, Jingang Wang (2010) - EP Patent [20070816581] invented controlled porosity osmotic tablet of high permeable drugs and preparation method thereof in which the objective of invention was CPOP tablets of Venlafaxine or Metoprolol, this invention simplified the preparation process increased the safety and reduced the production cost. It also showed that no laser drilling was required and preparation process thereof. Cellulose acetate was used as the semi permeable membrane, PEG 6000 as pore former and dibutyl sebacate as plasticizer.<sup>1</sup>
2. Chodankar Nand Kumar, Kashinath Patvardhan, Pramod Dattatrya (2009) Indian patent [226882] invented controlled porosity osmotic pump based drug delivery system of drugs having varying solubility characteristics, Diclofenac sodium, Pramipexole and Nifedipine prepared by direct compression and Pramipexole by push pull technology for once a day medication. The objective of this invention was to reduce the dosing frequency and achieve delivery of drugs over a period of 24 hours. The core of the tablets were prepared by adding fillers, swelling polymers, osmogens and lubricants. The core of the tablets were coated by coating polymers, plasticizers and pore forming agents.<sup>2</sup>
3. Gerald S. Rork, John L Haslam (1994) Patent WO [1994001093A1] invented controlled porosity osmotic pump of Enalapril pump, and it is surrounded by rate controlling water insoluble wall. The core of the tablet consists of Enalapril, sodium bi carbonate and lactose. It is enclosed by a wall, when it comes in contact with fluids it imbibes water and releases the drug forming pores and the objective of this invention was to release the drug at biological receptor sites over a constant period of time.<sup>3</sup>
4. John L Haslam, Gerald S. Rork (1989) US Patent [4886668A] invented multi particulate CPOP of Diltiazem L. Malate, the core consists of active ingredient and sodium bi tartrate, which has unique solubility characteristic in aqueous medium, and acts as osmotic pressure gradient across wall against external fluid. The wall consists of layer of controlled porosity which is permeable to both external fluid and aqueous solution of core. The drug is released from the system in pH independent manner by imbibing through walls at constant rate.<sup>4</sup>

5. Gregory A. McClelland et.al (1990) US Patent [4946686A] invented solubility modulated drug delivery system in which the drug release is by adding solubility modulating agents i.e complexing agents or surfactants which is surrounded by water insoluble core containing one pore former in the core. It is surrounded by water insoluble microporous wall surrounding the core composition comprising polymer.<sup>5</sup>
6. Avinash G. Thombre (1997) US Patent [5697922A] invented delivery device having encapsulated excipients in which the solubility modifier and an asymmetric membrane is present surrounding the device components.<sup>6</sup>
7. Edward M. Rudnic et.al (2000) –US Patent [6110498A] invented osmotic drug delivery system, in which the solubilizing agent and wicking agent enhances the flow of drug in solubilized form by the use of non swellable solubilizing agents. The drug is delivered through passages by osmosis in solubilized form but not by any physical form.<sup>7</sup>
8. Paul R Magruda, Brian Barclay (1988) US Patent [4751071A] invented an osmotic delivery system for controlled constant release rate of Salbutamol by modulated pulsed delivery system.<sup>8</sup>
9. Argaw kidane et.al (2006) -US Patent [8747897B2] invented the safe and effective method of sustain release of Trepstinil or its salt or derivatives as they have very short biological half life, release promoters are added for predictable release of drugs and the drug is released in controlled and pre determined rate, it is formulated as elementary osmotic pump. The drugs which have erratic drug release can be formulated by including release promoting agents in the formulation.<sup>9</sup>
10. Cardinal John, Herbig Scott M et.al (1997) US Patent [5612059] invented the osmotic device for controlled release through asymmetric membrane by diffusion and by osmotic pumping.<sup>10</sup>
11. David Swanson, David Edgren (1982)-US Patent [4326525A] invented osmotic device that improves delivery properties of agent in situ, for controlled delivery. The objective of invention was to deliver the poorly soluble drug and also too soluble drug in aqueous medium by improving its delivery from osmotic device. The other objective was to control the solubility of an agent in an osmotic device along with buffer that can interact to produce an agent with pre selected solubility.<sup>11</sup>
12. Nitin Dharmadhikari et.al (2003) –US Patent [20030219485A1] invented oral osmotic controlled drug delivery system for Glipizide. It consists of the drug in the core, hydrophilic polymer and excipients. The core was surrounded by SPM having a passage way for release. The other objective was using super disintegrants in the membrane having a passage way for release. It was a single compartment oral osmotic controlled drug delivery device.<sup>12</sup>
13. Gaylen M Zentner et.al (1986) EP Patent [0169105] invented controlled porosity osmotic pump consisting of atleast one active agent surrounded by water insoluble wall having fluid permeability and reflection coefficient of less than one, prepared from polymer permeable to water but not to solutes.<sup>13</sup>
14. John L. Haslam et.al (1989) US Patent [4880631] invented controlled porosity osmotic pump of Diltiazem L-Malate for controlled release, in which core consists of drug, buffer & sodium bitartrate. It is surrounded by rate controlling water insoluble wall having fluid permeability and reflection coefficient less than one.<sup>14</sup>
15. Arun D. Koparkar et.al (1994) US Patent [5284662] invented oral sustained release composition for slightly soluble drugs consisting of core and wall is surrounded around it, the core consists of Carbamazepine and effective amount of crystal habit modifier, a SPM wall around the core, permeable to water and a hole through SPM connecting the core with external environment.<sup>15</sup>
16. Zentner Gaylen. M et.al (1990) US Patent [4968507] invented osmotic pump comprising of atleast one drug surrounded by rate controlling water insoluble wall prepared from polymers, permeable to water but not to solute and one pH insensitive pore former dispersed throughout the wall.<sup>16</sup>
17. Chin Ming Chen et.al (1998) US Patent [5736159] invented controlled release formulation for water insoluble drugs in which a passageway is formed in situ, it is a single component osmotic tablet prepared by ordinary tablet compression techniques, it consists of compressed core with API, a water soluble osmotic agent, water soluble polymer & conventional excipients and a membrane around the core made up of modified water insoluble polymer and water soluble polymer to provide therapeutic levels with once a day medication with no pre formed aperture.<sup>17</sup>
18. George V Guittard et.al (1987) US Patent [4673405] invented osmotic system with instant drug availability, the objective of this invention was to provide controlled release of drug initially in increasing amount followed by constant amount of drug to receptor sites over prolong period of time. The SPM contains drug for instant delivery, a laminated wall of interior lamina and exterior lamina containing drug i.e available for immediate release as a burst of drug for eliminating the start up time required for certain drugs.<sup>18</sup>
19. William J. Curatolo (1991) US Patent [5030452] invented devices powered by lyotropic liquid crystals, it was devised for controlled release of drugs or mixtures made up of inner layer of lyotropic liquid crystals. The outer most layer consists of mixture of one or more drugs, lyotropic liquid crystals and water permeable polymer coating containing plurality of pores. Controlled delivery is effected by swelling of lyotropic liquid crystals.<sup>19</sup>

20. Felix Theeuwes, Atul. D. Ayer (1977) US Patent [4008719] invented osmotic systems having laminar arrangement for programming delivery of active agent, this system consists of wall made up of pair of laminae which is exterior laminae, made up of multiplicity of materials so that it is permeable to exterior fluid and maintains its integrity, interior lamina permeable to passage of external fluids and impermeable to agents. It consists of a compartment in which the drug is soluble in fluid and exhibits osmotic pressure gradient across the wall against fluid, during operation the compartment in the wall which is communicating with exterior of the device for dispensing the drug imbibing the water from the wall and releases drug dissolving and dispersing at controlled rate over a period of time.<sup>20</sup>

21. Anne Martine Billote et.al (2006) EP [1469826] invented osmotic delivery system, in which the osmotic tablet is made up of single layer of compressed core surrounded by water permeable layer for passageway. The core contains non – ripening drug which has a solubility per dose less than 1 ml<sup>-1</sup>, hydroxyl ethyl cellulose, osmogen and water permeable layer around the core and inner passage for delivery of drugs.<sup>21</sup>

22. Higuchi T, Leeper H (1973) US Patent [3760804] invented improved osmotic dispenser employing magnesium sulphate and magnesium chloride, the objective of this invention was to deliver the drug at osmotically controlled rate over a period of time depending on osmotic pressure created by aqueous solution of Mgcl<sub>2</sub> & Mgso<sub>4</sub> containing excess of magnesium sulphate in solid form against a hypotonic environment.<sup>22</sup>

23. J. Faour, Marcelo A. Coppari (2001) WO Patent [0151036] invented osmotic device within an osmotic device, it was the first device enclosed within a second osmotic device. The first device includes drug which is core surrounded by first SPM. The second osmotic device includes drug surrounding the first SPM and it surrounds the drug containing the composition. It also includes an immediate release outer coat.<sup>23</sup>

24. Patrick. S.L Wong et.al (1986) US Patent [4612008] invented osmotic device with dual thermodynamic activity, it consists of wall formed in a part of semi permeable material surrounding compartment, it contains first osmotic composition containing drug and second different osmotic composition. A passageway in wall connects the first composition to the exterior of the system.<sup>24</sup>

### **Classification of osmotic drug delivery system:**

#### **Implantable:**

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

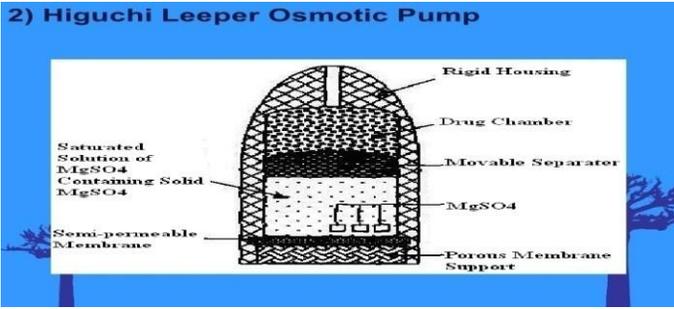
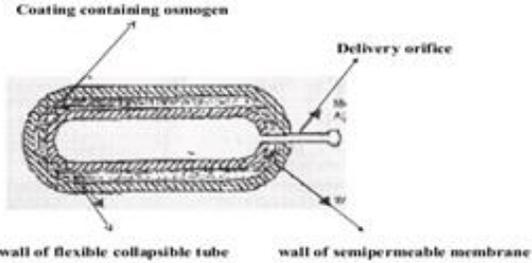
#### **Oral Osmotic Pump:**

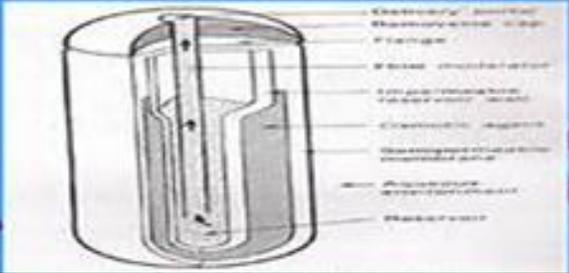
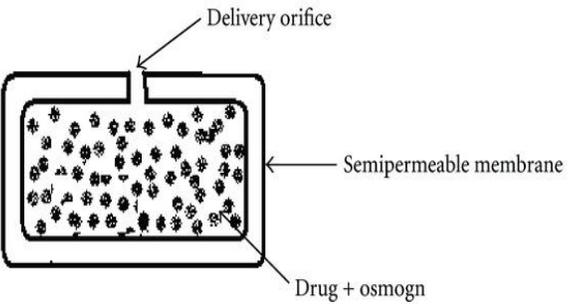
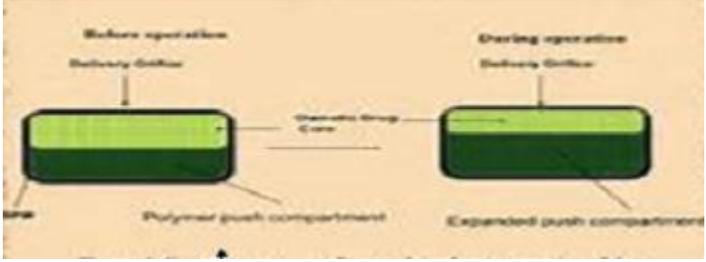
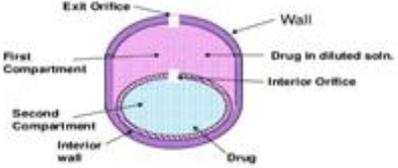
1. **Single Chamber Osmotic Pump:**  
Elementary osmotic pump (EOP)
2. **Multiple Chamber Osmotic Pump:**
  - Push pull osmotic pump (PPOP)
  - Osmotic pump with non expanding second chamber

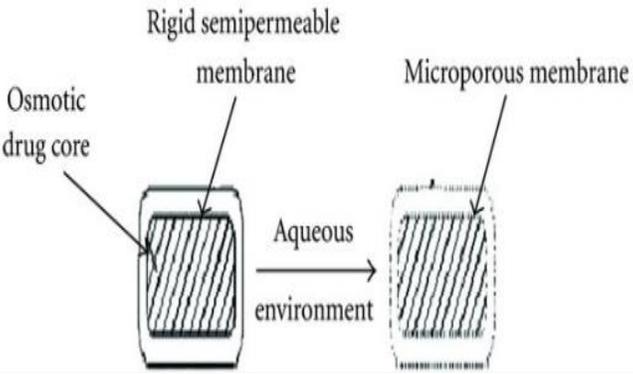
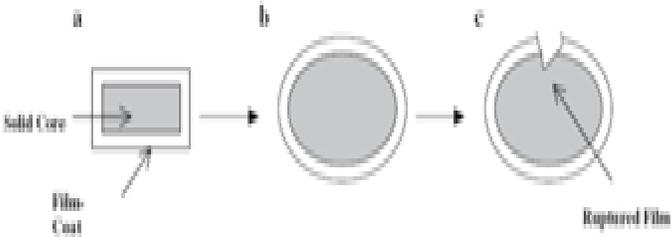
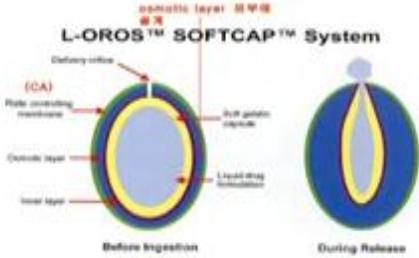
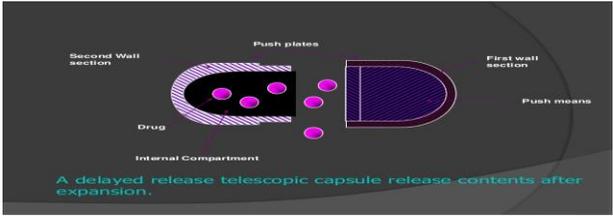
#### **Specific Types:**

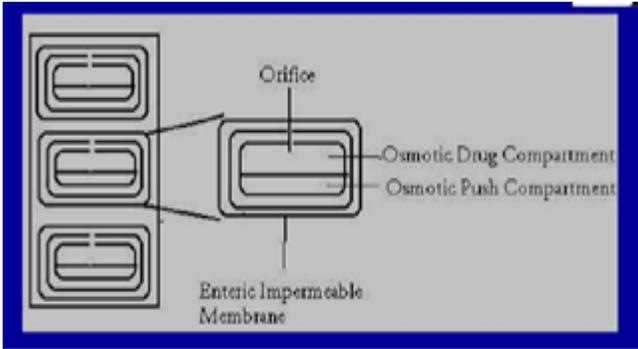
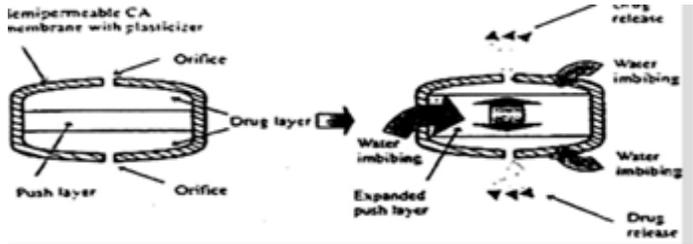
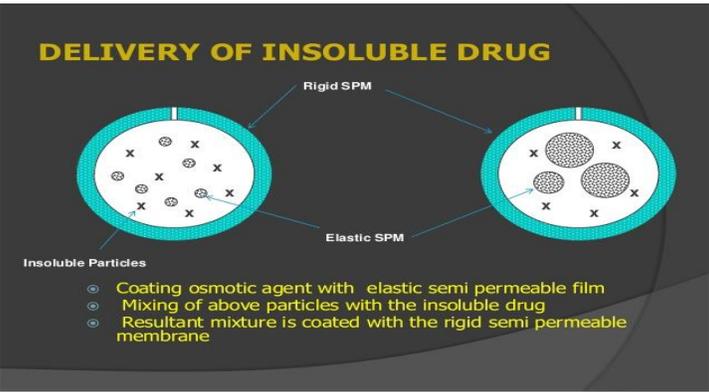
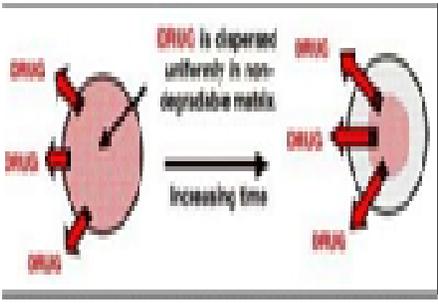
1. Controlled porosity osmotic pump (CPOP)
2. Osmotic bursting osmotic pump
3. Liquid OROS-
  - a) L OROS hard cap
  - b) L OROS Soft cap
  - c) Delayed liquid bolus delivery system.
4. Telescopic capsule for delayed delivery osmotic system
5. OROS-CT (Colon targeting)
6. Sandwiched oral therapeutic system (SOT)
7. Osmotic pump for insoluble drugs
8. Monolithic osmotic system and OSMAT
9. Effervescent activity based osmotic system
10. Multilayer osmotic pump
11. Multi particulate delayed release system.

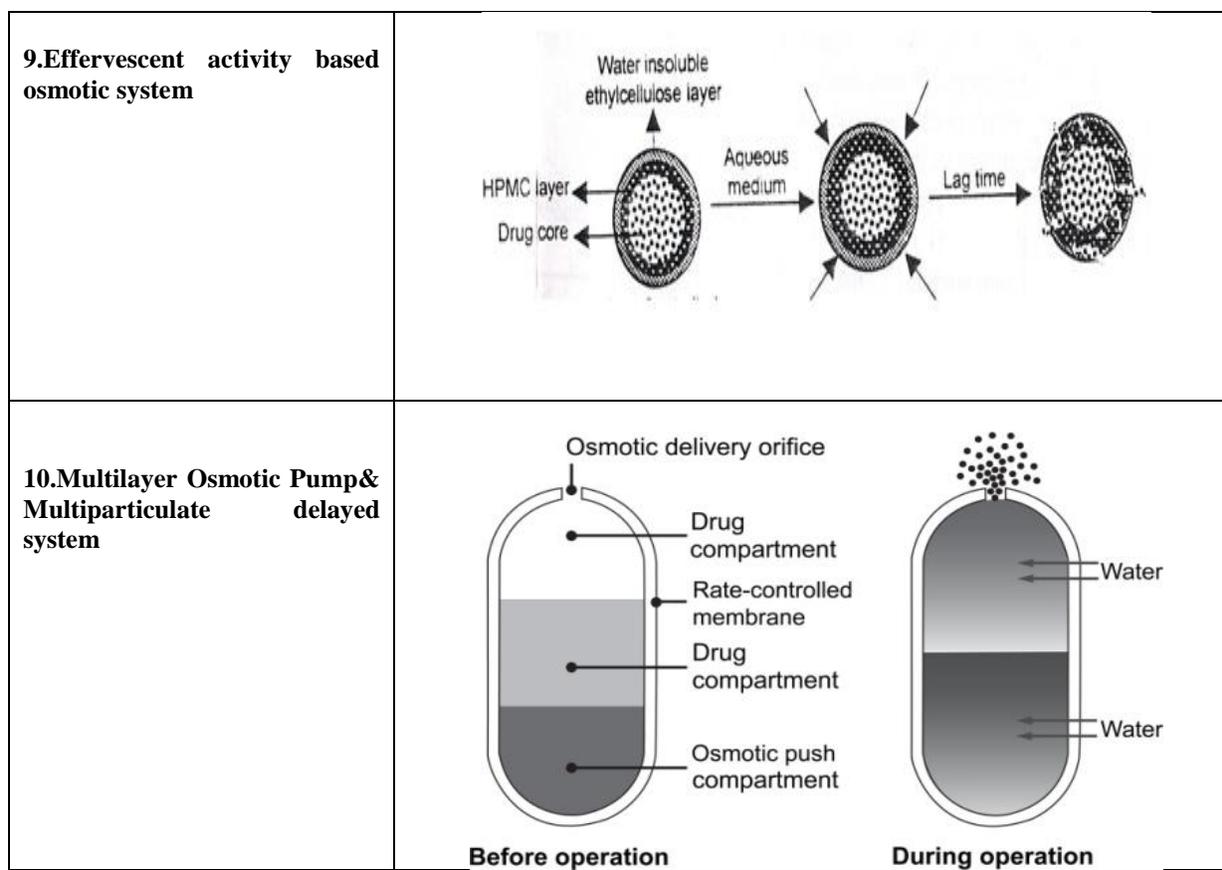
Table 3: Types of osmotic pumps

Names	Osmotic Pumps
<p><b>Implantable:</b>  <b>1. The Rose And Nelson Pump</b></p>	 <p>The diagram illustrates the Rose Nelson pump, an implantable osmotic pump. It consists of a cylindrical device with three main chambers: a Water Chamber, a Salt Chamber, and a Drug Chamber. A Rigid Semi permeable membrane separates the Water Chamber from the Salt Chamber. An Elastic Diaphragm separates the Salt Chamber from the Drug Chamber. A Delivery orifice is located at the end of the Drug Chamber. The diagram shows the pump in two states: one where the diaphragm is flat and one where it is curved due to osmotic pressure.</p>
<p><b>2.Higuchi Leeper pump</b></p>	 <p>The diagram shows the Higuchi Leeper osmotic pump. It features a Rigid Housing containing a Drug Chamber. A Movable Separator is positioned between the Drug Chamber and a layer of MgSO4. Below the MgSO4 is a Porous Membrane Support, which is in contact with a Semi-permeable Membrane. The pump is surrounded by a Saturated Solution of MgSO4 Containing Solid MgSO4.</p>
<p><b>3.Higuchi Theeuwes pump</b></p>	<p><b>Higuchi-Theeuwes osmotic pump</b></p> <p>➤ It is another simplest modified version of Rose &amp; Nelson pump.</p>  <p>The diagram illustrates the Higuchi-Theeuwes osmotic pump. It consists of a flexible collapsible tube with a wall of semipermeable membrane. The tube is coated with a coating containing osmogen. A Delivery orifice is located at one end of the tube. The diagram shows the tube in two states: one where it is collapsed and one where it is expanded due to osmotic pressure.</p>
<p><b>4.Implantable Mini Osmotic pump</b></p>	

	<p>4) Implantable mini osmotic pump: Alzet pump.</p> 
<p><b>1. Single Chamber Osmotic Pump:</b> Elementary Osmotic pump (EOP)</p>	
<p><b>2. Multiple chamber osmotic pump:</b> a) Push Pull osmotic pump (PPOP)</p>	
<p>b) Osmotic Pump with Non Expanding Second Chamber</p>	

<p><b>Specific Types:</b>  <b>1. Controlled Porosity Osmotic Pump (CPOP)</b></p>	
<p><b>2. Osmotic Bursting pump</b></p>	
<p><b>3. Liquid OROS</b></p>	
<p><b>4. Telescopic Capsule for Delayed Delivery Osmotic system</b></p>	 <p>A delayed release telescopic capsule release contents after expansion.</p>

<p><b>5. OROS-CT (Colon Targeting)</b></p>	
<p><b>6. Sandwiched Oral Therapeutic System (SOT)</b></p>	
<p><b>7. Osmotic Pump for Insoluble drugs.</b></p>	<p style="text-align: center;"><b>DELIVERY OF INSOLUBLE DRUG</b></p>  <ul style="list-style-type: none"> <li>⊙ Coating osmotic agent with elastic semi permeable film</li> <li>⊙ Mixing of above particles with the insoluble drug</li> <li>⊙ Resultant mixture is coated with the rigid semi permeable membrane</li> </ul>
<p><b>8. Monolithic Osmotic System and OSMAT</b></p>	



### Evaluation of cpop tablets

- Thickness
- Diameter
- Weight variation
- Hardness
- Friability
- Disintegration
- Drug content uniformity
- In vitro Dissolution studies.

### Evaluation of formulation variables:

- Effect of pH.
  - Effect of agitation intensity.
  - Effect of osmotic pressure.
  - Effect of amount of pore former on drug release.
  - Effect of coating thickness.
  - Burst strength.
- Curve fitting analysis (Kinetics and mechanism of drug release).
  - Study of surface morphology by scanning electron microscopy.
  - Stability studies.

### Conclusion

The discovery of new drugs which are to delivered at precise and controlled rate can be administered by osmotic delivery systems. Recent advances include controlled porosity osmotic pump, L – OROS pumps, and sandwiched osmotic tablet. In future pulsatile delivery systems would be successfully produced. The release of drug follows zero order kinetics and it is safer than other conventional forms.

## References

1. Haisong Jiang, Jingang Wang. "Controlled Porosity Osmotic Pump Tablet Of High Permeable Drugs and The Preparation Method Thereof", EP Patent 20070816581, 18 Nov 2010.
2. Chodankar Nand Kumar, Kashinath, Pat Vardhan, Pramod Dattatrya. "Controlled Porosity Osmotic Pump Based Drug Delivery System", Indian Patent 226882, 6 Mar 2009.
3. Gerald S. Rork, John L. Haslam. "Controlled Porosity Osmotic Enalapril Pump", WO Patent 1994001093A1, 20 Jan 1994.
4. John L Haslam, Gerald S. Rork. "Multiparticulate Controlled Porosity Osmotic Pump", US Patent 4886668A, 12 Dec 1989.
5. Gregory A .Mc Clelland, Gaylen M Zentner. "Solubility Modulated Drug Delivery System", US Patent 4946686A ,7 Aug 1990.
6. Avinash G Thombre. "Delivery Device Having Encapsulated Excipients", US Patent 5697922A, 16 Dec 1997.
7. Edward M. Rudnic, Beth A. Burnside, Henry H. Flanner et al. "Osmotic Drug Delivery System", US Patent 6110498A, 29 Aug 2000.
8. Paul R Magruda, Brian Barclay et al. "Composition Comprising Salbutamol",US Patent 4751071A ,14 June 1988.
9. Argaw Kidane, Padmanabh P Bhatt. "Osmotic Drug Delivery System", US Patent 8747897B2,10 Jun 2014.
10. Cardinal John, Herbig Scott M et al. "Use Of Asymmetric Membranes In Delivery Devices ", US Patent 5612059, 18 March 1997.
11. David Swanson, David Edgren. "Osmotic Device That Improves Delivery Properties of Agent In Situ", US Patent 4326525A, 27 April 1982.
12. D. N. Bhalachand, M.A Prabakar. "Oral osmotic controlled drug delivery system", US Patent 2003219485,27 Nov 2003.
13. Gaylen M .Zentner, Gerald S .Rork, J. Himmelstein. "Controlled Porosity Osmotic Pump", EP 0169105A2, 22 Jan 1986.
14. John L Haslam, Gerald S Rork. "Controlled Porosity Osmotic Pump", US Patent 4880631A, 14 Nov 1989.
15. A.D .Koparkar, S.B.Shah. "Oral osmotic system for slightly soluble active agents", US Patent 5,284,662, Feb.8, 1994.
16. G.M Zentner, G.S Rork, K.J. Himmelstein. "Controlled porosity osmotic pump", US Patent 4,968,507,Nov .6,1990.
17. C. Chen, D.Lee, J.Xie. "Controlled release formulations for water insoluble drugs in which a passageway is formed in situ",US Patent 5,736,159, April 7,1998.
18. G.V. Guittard, J.C Deters, F. Theeuwes, R.Cortese. "Osmotic system with instant drug availability", US Patent 4,673,405,June 16,1987.
19. W.J. Curatolo. "Dispensing devices powered by lyotropic liquid crystals", US patent 5,030,452, Jan. 12, 1989.
20. F. Theeuwes, A.D.Ayer. "Osmotic system having laminar arrangement for programming delivery of active agent", US Patent 4,008,719, Feb.22, 1977.
21. Biliote Anne Martine. "Osmotic delivery system", European Patent EP 1469826B1,2006.
22. T. Higuchi, H.M Leeper. "Improved osmotic dispenser employing Magnesium sulphate and Magnesium chloride", US Patent 3,760,804 in 1973.
23. J. Faour, M.A Coppari, Phoenix (Osmotica). "Osmotic device within an osmotic device", W.O Patent 0151036,19 July 2001.
24. P.S.L Wong, B.Barclay, JC Deters, F Theeuwes. "Osmotic device with dual thermodynamic activity", US Patent 4,612,008,16 Sept. 1986.
25. P. Sandhya, Hafsa Siddiqua, Ayesha Sultana et al. "Formulation And Evaluation of Oral Controlled Release Osmotic Tablets Of Glimperiride", IOSR Journal of Pharmacy and Biological Sciences, Sept-Oct 2013; Vol 7(4): 01- 07.
26. Ayesha Sultana, D. Varun. "Controlled Porosity Osmotic Pump (CPOP)-The most promising strategy based system review", World Journal of Pharmacy and Pharmaceutical Sciences, Dec 2016; Vol 6(1): 353-367.

27. *Chinmaya Keshari Sahoo et al. "A review on Controlled Porosity Osmotic Pump tablets and its evaluation"., Bulletin of Faculty of Pharmacy, Cairo university(Elsevier),Oct 2015;1-11.*
28. *Robert C, Gupta SK. "Clinical spectrum of the Osmotic - Controlled release oral delivery system (OROS),An advanced oral delivery form"., Current Technology of Medical Research and Opinion ,2006; Vol 22(10): 1879- 1892.*
29. *D. Ezra, M Molho et al. "Atenolol in Hypertension: A Cardiosselective Drug"., CHEST Journal,2015.*
30. *"Heart Diseases And Strokes Statistics 2017 At A Glance"., American Heart Association And American Stroke Association.1-5.*
31. *AM Kaushal, S. Garg. "An update on osmotic drug delivery patents"., Pharmaceutical Technology, 2003; 38-44.*
32. *X Li, B.R. Jasti. "Osmotic controlled drug delivery systems, in Design of Controlled Release of drug delivery systems"., McGraw Hill, 2006; 203-229*