A REVIEW: OSMOTIC DRUG DELIVERY SYSTEM

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ABSTRACT

Conventional oral drug delivery systems supply continues release of drug, which cannot release of the drug and effective concentration at the target site. Drug can be delivered in a controlled manner over a long period of time by the process of osmosis. Osmotic devices are the most promising technique for controlled drug delivery. Osmotic drug delivery system is one among the controlled drug delivery employed orally and also as an implantable devices. These systems utilize osmosis as the major driving force for drug release. Various patents available for osmotic drug delivery system like Rose-Nelson pump, Higuchi leeper pump, Higuchi Theeuwes pump, Elementary Osmotic pump etc. Various techniques available for preparation of Osmotic Drug Delivery System include Push pull osmotic pump, Osmotic brusting osmotic pump, Liquid oral osmotic system, Sandwiched osmotic tablets, Delayed delivery osmotic device, Monolithic osmotic system and Controlled porosity osmotic pump. Osmotic drug delivery devices are composed of an osmotically active drug core, which is surrounded by a rate controlling membrane. Osmotic drug delivery systems differ from diffusion based systems in that the delivery of the active agents is driven by an osmotic gradient rather than the concentration of drug in the device.

KEYWORDS: Osmotic drug delivery, Osmosis, Osmotic gradient, various techniques for osmotic drug delivery.
INTRODUCTION
Oral controlled release (CR) systems most popular amongst all the drug delivery system. Because of pharmaceutical agents can be delivered in a controlled manner over a long period. Conventional oral drug delivery system supply continues release of drug, which cannot control the release of the drug and effective concentration at the target site. The bioavailability of drug from these formulations may vary significantly, depending on factor such as physico-chemical properties of the drug, presence of excipients, various physiological factors such as the presence or absence of food, pH of the GI tract, GI motility etc. To overcome this problem a number of design option are available to control or modulate the drug release from a dosage form. Majority of oral dosage form fall in the category of matrix, reservoir or osmotic system. There has been increasing interest in the development of osmotic devices over the past 2 decades, due to reservoir systems have a drug core surrounded coated by the rate controlling membrane. Drug delivery from this system is not influenced by the different physiological factors within the gut lumen, and the release characteristic can be predicted easily from the known properties of the drug and the dosage form. Drug release from these systems is independent of pH and other physiological parameter to a large extent and it is possible to modulate the release characteristic by optimizing the properties of drug and system.\textsuperscript{[1, 2]}

Osmotically Controlled Drug Delivery System (OCDDS) Osmotic devices are the most calculable controlled drug delivery system (CDDS) and can be employed as oral drug delivery systems. Osmotic pressure is used as the driving force for these systems to release the drug in a controlled pattern. Osmotic pump tablet (OPT) generally consists of a core including the drug, an osmotic agent, other excipients and semi permeable membrane coat.\textsuperscript{[3]}

ADVANTAGES\textsuperscript{[3, 4]}

- Easy to formulate and simple in operation.
- Deliveries may be delayed or pulsed if desired.
- Prolonged therapeutic effect with uniform blood concentration.
- Improve patient compliance with reduced frequency.
- Drug release is independent of gastric pH and hydrodynamic condition.
- The release mechanisms are not dependent on drug.
- They are well characterized and understood.
- A high degree of in-vitro and in-vivo correlation (IVIVC) is obtained in osmotic systems.
The release from osmotic system is minimally affected by the presence of food in gastrointestinal tract.

The release rate of osmotic systems is highly predictable and can be programmed by modulating the release control parameters.

**DISADVANTAGES**<sup>[3,4]</sup>

- Expensive.
- Dose dumping.
- Rapid development of tolerance.
- Size hole is critical.
- Retrieval therapy is not possible in the case of unexpected adverse events.
- If the coating process is not well controlled there is a risk of film defects, which result in dose dumping.

**OSMOSIS**<sup>[1]</sup>

Principle

Osmotic systems utilize the principle of osmotic pressure for the delivery of drugs. Conventionally, osmosis can be defined as the net movement of water across a selectively permeable membrane driven by a difference in osmotic pressure across the membrane that allows passages of water but casts off solute molecules or ions. The first osmotic effect was reported by Abbe Nollet in 1748. Later in 1877, Pfeffer performed an experiment using semi-permeable membrane to separate sugar solution from pure water. In 1886, Vant hoff identified an underlying proportionality between osmotic pressure, concentration and temperature.

The relationship can be described by following equation.

\[ \pi = \phi c RT \]

Where,

- \( \pi \) = Osmotic pressure,
- \( \phi \) = 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.

COMPONENTS OF OSMOTIC DRUG DELIVERY SYSTEMS\(^{[5,6]}\)

- Osmotic pumps contain a drug semi permeable membrane.
- The semi permeable membrane usually contains a plasticizer and in some cases surfactant and also pore forming agents.
- Parts from the above materials, common tableting aids such as lubricants, binder, diluents, glidants, wetting agents etc.

a. DRUGS\(^{[1]}\)
- Highly potent drug
- Short biological half-life [2 -6 hrs]
- Required for prolonged treatment

b. SEMIPERMEABLE MEMBRANE\(^{[14,15]}\)
- Cellulose acetate is a commonly used semi-permeable polymer for the preparation of osmotic pumps.
- It is accessible in different acetyl content of 32\% and 38\%.
- Polymers are agar acetate, amylase triacetate, poly-(vinyl-methyl)-ether copolymers and selectively permeable poly-(glycolic-acid) and poly-(lactic-acid) derivatives can be used as semi-permeable film forming materials.

c. HYDROPHILIC AND HYDROPHOBIC POLYMERS\(^{[5,6]}\)
- These polymers are used in the formulation development of osmotic system for making drug contain matrix convention.
- The highly water soluble compounds can be co-entrapped in hydrophobic matrices and moderately water soluble compounds can be co-entrapped hydrophilic matrices to obtain more controlled release.
- The non-swellable polymers are used in case of highly water-soluble drugs.
Ionic hydrogels such as sodium carboxymethyl cellulose, carboxy methylcellulose, Hydroxy propyl MC, high molecular weight poly-(vinyl pynolidone) and hydrophobic polymers such as EC and wax materials used for this purpose.

d. **WICKING AGENTS**\(^{[14, 15]}\)

- Wicking agent is defined as a material with the ability to draw water into porous network of a delivery device.
  - A wicking agent is of either swellable or non-swellable nature.
  - They are characterized by having the ability to undergo physiosorption with water.
  - The function of the wicking agent is to carry water to surface inside the core of the tablet, thereby creating channels or a network of increased surface area.
  - Materials, which suitably for act as wicking agents include colloidal silicon-di-oxide, kaolin, titanium-di-oxide, alumina, sodium lauryl sulphate (SLS), colloidal silica and PVP are non swellable wicking agents.

e. **SOLUBILISING AGENTS**\(^{[14, 15]}\)

- Agents that inhibit crystal formation of the drugs or otherwise act by complexation with the drugs.
  - Eg – PVP, PEG-8000, cyclodextrins.
  - A high HLB micelle-forming surfactant, particularly anionic surfactants.
  - Eg – tween-20, 60 and 80, poly-oxy-ethylene or poly-ethylene containing surfactants and other long chain anionic surfactant such as SLS
  - Citrate esters and their combinations with anionic surfactants.
  - Eg – alkyl esters particularly tri ethyl citrate.

f. **OSMOGENS**\(^{[7, 8]}\)

- Osmogen are essential ingredients of the osmotic formulations.
  - Include inorganic salts and carbohydrates.
  - Generally combination of osmogen is used to achieve optimum osmotic pressure inside the system.

g. **SURFACTANTS**\(^{[9]}\)

- Surfactants are particularly useful when added to wall forming material.
  - Typical surfactants are Poly-oxy-ethylenated glyceryl lecinoleate, Poly-oxy-ethylenated castor oil having ethylene oxide, glyceryl laureates and glycerol.
h. COATING SOLVENTS\textsuperscript{[9]}
   - Solvent suitable for making polymeric solution that is used for manufacturing the wall of the osmotic device include inert inorganic and organic solvents.
   - Typical solvents include methylene chloride, acetone, methanol, ethanol, isopropyl alcohol, butyl alcohol, ethyl acetone, cyclo-hexane, carbon tetrachloride, water etc and the mixture of solvent such as acetone : methanol (80:20), acetone : ethanol (80:20).

i. PLASTICIZERS\textsuperscript{[9]}
   - Increase the flexibility and permeability of the fluids.
   - 0.001 to 50 parts of a plasticizer or a mixture of plasticizers are incorporated into 100 parts of wall forming materials.
   - PLASTICISERS are triethyl citrate and other citrates, dialkyl phthalates and other phthalates, tristyl phosphates and other phosphates, acetates, glycolate, glycerolate, benzoate, sulphonamides and halogenated phenyls.

j. FLUX REGULATORS\textsuperscript{[9]}
   - Flux regulators are added to the wall forming material. It assists in regulating the fluid permeability of flux through wall.
   - They also increase the flexibility and porosity of the lamina.
   - Usually, from 0.001 parts to 50 parts or high weight fraction of flux regulators can be used.
   - Poly-hydric alcohols such as poly alkylene glycols and low molecular weight glycols such as poly propylene, poly butylenes and poly amylene etc; can be used as flux regulators.

k. REFORMING AGENTS\textsuperscript{[9]}
   - 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.
   - These pore-forming agents cause the formation of microporous membrane
   - For example – alkaline metal salt such as sodium chloride, potassium chloride and potassium phosphate.
   - Alkaline earth metals such as CaCl\textsubscript{2} and carbohydrates such as glucose, sucrose, fructose, lactose, maltose, mannitol and polyols such as polyvinyl pyrolidone and polyhydric alcohols can be used as pore forming agents.
CLASSIFICATION OF OSMOTIC DRUG DELIVERY SYSTEM\textsuperscript{[10]}

They fall into two categories

1. IMPLANTABLE
   - The rose and nelson pump
   - Higuchi leeper pump
   - Higuchi theuwes pump
   - Implantable mini-osmotic pump

2. ORAL OSMOTIC PUMP
   - Single chamber osmotic pump
   - Multi chamber osmotic pump
   - Osmotic Pump with Non Expanding Second Chamber

3. SPECIFIC TYPES
   - Controlled porosity osmotic pump
   - Liquid OROS
   - Delayed Delivery Osmotic device
   - Osmotic pump for insoluble drugs
   - Monolithic osmotic system

1. IMPLANTABLE
   a. The Rose and Nelson Pump\textsuperscript{[5]}

Rose and Nelson were 2 Australian physiologists interested in the delivery of drug to the gut of sheep and cattle. The pump consisted of three chambers: a drug chamber, a salt chamber containing excess solid salt and water chamber. The drug and water chamber are separated by a rigid semi permeable membrane. The difference in osmotic pressure across the membrane moves water from chamber into the salt chamber. The volume of the salt chamber increases because of this water flow, which distends the latex diaphragm separating the salt and drug chamber, thereby pumping drug out of the device.

The pumping rate of the Rose-Nelson pump is given by the equation

\[
\frac{dM}{dt} = \left(\frac{dv}{dt}\right)C
\]

Where,
\(dM / dt\) – drug release rate,
\(dv / dt\) – volume flow of water in to salt chamber,
C – Concentration of drug in the drug chamber.

b. Higuchi Leeper Pump[1]

Higuchi Leeper pump is widely used for veterinary use. This type of pump is either swallowed or implanted in the body of animal for delivery of growth hormones or antibiotic. Higuchi Leeper pump consist of rigid housing and semi permeable membrane. Recent modification in Higuchi-Leeper pump accommodated pulsatile drug delivery.

![Diagram of Higuchi Leeper Pump](image)

In this device the rigid housing is made up of semi permeable membrane which is enough strong to with the pumping pressure developed inside the device due to permeation of water. The drug loaded only to the prior of application of device. The release of drug from device can be controlled by salt used in chamber, the permeability characteristic of outer membrane and orifice. Osmotic pump of this form are available under trade name “Alzet”. A mixture of citric acid and sodium bi carbonate in salt chamber in presence of water generate carbon di-oxide gas. Which exert a pressure on the elastic diaphragm, eventually delivers the drug from device.

d. Implantable Mini Osmotic Pump[1]

Implantable Mini osmotic pump composed of three concentric layers-the drug reservoir, the osmotic sleeves and the rate controlling semi permeable membrane. The additional
component called flow moderator is inserted into the body of the osmotic. The inner most compartment of drug reservoir which is surrounded by an osmotic sleeve, a cylinder containing high concentration of osmotic agent. The osmotic sleeve is covered by a semi permeable membrane when the system is placed in aqueous environment water enters the sleeve through semi permeable membrane, compresses the flexible drug reservoir and displaces the drug solution through the flow moderator.

These pumps are available with variety of delivery rates between 0.25 to 10 ml per hour and delivery duration between one day and four weeks.

2. ORAL OSMOTIC PUMP

a. Single chamber osmotic pump (Elementary osmotic pump)\cite{4,11}

Elementary osmotic pump works on the same mechanism as the impala table pumps it is simplest possible form of osmotic pump as it does not require special equipment and technology. It was developed in the year 1975 by Theeuwes. The EOP consist of single layered table core containing a water soluble drug with or without other osmotic agent. A semi permeable membrane surrounds the tablet core. Normally the EOP delivers 60-80% of its content at a constant rate and there is a short lag time of 30-60 min as the system hydrates before zero order drug release from the EOP is obtained.

b. Multi chamber osmotic pump (Push pull osmotic pump)\cite{4}

Push pull osmotic pump is a modified EOP through, which it is possible to deliver both poorly water-soluble and highly water soluble drugs at a constant rate. This system resembles a standard bilayer coated tablet. One layer (upper layer) contains drug in a formulation of
polymeric, osmotic agent and other tablet excipients. This polymeric osmotic agent has the ability to form a suspension of drug in situ. When this tablet later imbibes water, the other layer contains osmotic and colouring agents, polymer and tablet excipients. These layers are formed and bonded together by tablet compression to form a single bilayer core. The tablet core is then coated with semi permeable membrane. After the coating has been applied, a small hole is drilled through the membrane by a laser or mechanical drill on the drug layer side of the tablet.

c. Osmotic Pump with Non Expanding Second Chamber[4]
The second category of multi-chamber devices comprises system containing a non-expanding second chamber. This group can be divided into two sub groups, depending on the function of second chamber. In one category of these devices, the second chamber is used to dilute the drug solution leaving the devices. This is useful because in some cases if the drug leaves the oral osmotic devices a saturated solution, irritation of GI tract is a risk.

4. SPECIFIC TYPES
a. Controlled porosity osmotic pump[3,12]
The controlled-porosity osmotic pump tablet (CPOP) is a spray-coated or coated tablet with a semi permeable membrane (SPM) containing leachable pore forming agents. They do not have any aperture to release the drugs; drug release is achieved through the pore, which is formed in the semi permeable wall in situ during the operation. In this system, the drug after dissolution inside the core is released from the osmotic pump tablet by hydrostatic pressure and diffusion through pores created by the dissolution of pore formers incorporated in the membrane. The hydrostatic pressure is created either by an osmotic agent or by the drug itself or by a tablet component after water is imbibed across the semi permeable membrane.
b. Liquid OROS\(^4\)

Liquid OROS are drawn to deliver drugs as liquid formulation and combine the benefits of extended release with high bioavailability. They are of three types

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

c. Delayed Delivery Osmotic device\(^4\)

Due to their semi permeable walls, an osmotic device intrinsically show lag time before drug delivery begins. Although this characteristic is usually cited as a disadvantage, it can be used advantageously. The delayed release of certain drug [drugs for early morning asthma or arthritis] may be beneficial.

d. Osmotic pump for insoluble drugs or Lipid osmotic pump\(^11\)

The device concerns an osmotic agent for dispensing beneficial active agent that has poor solubility in water. The core of the system comprises a beneficial amount of a substantially water – insoluble active agent, which is lipid soluble or lipid-wettable; a sufficient amount of water insoluble lipid carrier of the drug and agent to ensure the release of the lipid carrier of the drug and agent to ensure the release of the lipid carrier of the drug from the pump. The water insoluble wall is micro porous and is wetted by lipid carrier. The device is prepared by first dissolving the drug of interest in the lipid vehicle. The osmogen (Sodium chloride) is dispersed in the melted lipid and then quenched-cool to form a lump that are broken and made into tablet. The micro porous is coated at a moderate flow of unheated ambient air.

e. Monolithic osmotic system\(^4,12\)

It constitutes a simple dispersion of water-soluble agent in polymer matrix. When the system comes in contact with the aqueous environment water inhibitions by the active agent takes place rupturing the polymer matrix capsule surrounding the drug, thus liberating it to the outside environment. Initially this process occurs at the outer environment of the polymeric matrix, but gradually proceeds towards the interior of the matrix in a serial fashion.

f. OSMAT\(^4\)

It is a novel osmotically driven matrix system, which utilizes the hydrophilic polymers to swell, and gel in aqueous medium forming a semipermeable membrane in-situ releases from such a matrix system containing an osmogen could, therefore be modulated by the osmotic
phenomenon. OSMAT is resulting in a quantum improvement in drug delivery from swellable matrix system. OSMAT produces controlled drug release with adequate delivery rates in an agitation in dependent manner. Thus OSMAT represent simple, versatile, and easy to fabricate osmotically driven controlled drug delivery system based upon low cost technology.

FACTORS AFFECTING DRUG RELEASE RATE\textsuperscript{[16, 17]}

- **Solubility**
  Medicaments for osmotic delivery should have water solubility in the desired range to get optimize drug release. By modulating the solubility of these drugs within the core, effective release patterns may be obtained for the drugs, which might otherwise appear to be poor candidate for osmotic delivery.

Solubility-modifying approaches

- Use of swellable polymers – Polyethylene Oxide have uniform swelling rate which causes drug release at constant rate.
- Use of effervescent mixtures – Mixture of citric acid and sodium bicarbonate which creates pressures in the osmotic system and ultimately controls the release rate.
- Use of wicking agents – These agents may enhance the surface area of drug with the incoming aqueous fluid.
  Eg – Sodium lauryl sulphate, Colloidal silicon dioxide etc.
- Use of encapsulated excipients – Solubility modifier excipients used in form of mini-tablet coated with rate controlling membrane.
- Use of Cyclodextrin derivatives – Increases solubility of poorly soluble drugs. The same occurrence can also be used for the osmotic systems.
- Use of crystal habit modifiers – 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. Different excipients can be used to modulate the solubility of APIs with different mechanisms like saturation solubility, pH dependent solubility. Example – Organic acids, buffering agents etc.

- **Size of delivery orifice:**
  To achieve an optimal zero order delivery profile, the cross section area of the orifice must be smaller than a maximum size to minimize drug delivery by diffusion through the orifice. The typical orifice size in osmotic pumps ranges from 600µ to 1 mm.
Methods to create a delivery orifice in the osmotic tablet coating are –

- Mechanical drill
- Laser drill – Co₂ laser beam (10.6µ) and low costs
- Use of leachable substance in the semi-permeable coating.
  Eg- controlled porosity osmotic pump
- Indentation that is not covered during the coating process –
  Indentation is made in core tablets by using modified punches having needle on upper punch. This indentation is not covered during coating process which acts as a path for drug release in osmotic system.

- EVALUATION OF OSMOTIC TABLET[^7,18]
  I. Evaluation of powder
  - Weight of Powder
  - Bulk density
  - Tapped density
  - Carr’s index
  - Angle of repose

  II. Evaluation of Osmotic tablet
  - Hardness
  - Thickness
  - Friability
  - Weight uniformity
  - Drug content
  - In – vitro dissolution study

  III. Effect of Osmotic pressure
  IV. Effect of pH on drug release
  V. Stability study
  VI. Curve fitting analysis
  VII. Zero order release kinetic
  VIII. First order release kinetic
REFERENCES


