“AN OVERVIEW ON OSMOTIC DRUG DELIVERY SYSTEM”

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Osmosis, semipermeable membrane, osmotic pump, zero order, osmotic agent.

Abstract

Conventional drug delivery systems have little control over their drug release and almost no control over the effective concentration at the target site. The kind of dosing pattern may result in constantly changing, unpredictable plasma concentrations. The number of marketed oral osmotically driven systems (OODS) has doubled in the last 10 years. Osmotic devices which are tablets coated with walls of controlled porosity are the most promising strategy based systems for controlled drug delivery. Osmotically controlled drug delivery systems (OCDDS) utilize osmotic pressure for controlled delivery of active agent(s). In contrast to common tablets, these pumps provide constant (zero order) drug release rate. Factors influencing the design of osmotic controlled drug delivery systems such as solubility and osmotic pressure of the core components, size of delivery orifice, and nature of the rate controlling membrane. The present review highlights an overview of OCDDS, types of oral osmotic drug delivery system, factors affecting the drug delivery system and marketed products.

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INTRODUCTION:
Novel drug delivery systems (NDDS) are the key area of pharmaceutical research and development. Majority of oral CR dosage forms fall in the category of matrix, reservoir or osmotic systems. Osmotically controlled drug delivery systems (OCDDS) is one of the most promising drug delivery technology. Osmotic devices are the most reliable controlled drug delivery systems (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 manner. Osmotic pump tablet (OPT) generally consists of a core including the drug, an osmotic agent, other excipients and semipermeable membrane coat. Drugs can be delivered in a controlled pattern over a long period of time by the controlled or modified release drug delivery systems they include dosage forms for oral and transdermal administration as well as injectable and implantable systems. Osmotic drug delivery systems release the drug with the zero order kinetics which does not depend on the initial concentration and the physiological factors of GIT.

Development of osmotic drug delivery systems was founded by Alza Corporation of the USA (now merged with Johnson & Johnson, USA) and it holds major number of the patents and also markets several products based on osmotic principle. The first and most important osmotic delivery system patent (U.S. Patent 3,845,770) assigned to Alza in 5 November 1974 and covering Theeuwes original elementary osmotic pump design. Indomethacin (Osmosin®) and Phenyl Propanolamine (Acutrim®) are the first two marketed osmotic based products. (3)

Basic concepts

Osmosis
Osmosis is defined as the process of movement of solvent molecules from lower concentration to higher concentration across a semi permeable membrane.

Osmotic pressure
It 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.

Principle of Osmosis
Osmosis can be defined as the spontaneous movement of a solvent from a solution of lower solute concentration to a solution of higher solute concentration through an ideal semipermeable membrane, which is permeable only to the solvent but impermeable to the solute. The pressure applied to the higher concentration side to inhibit solvent low is called the osmotic pressure.
Advantages and Disadvantages of Osmotic Controlled Drug Delivery systems\(^{(9-15)}\)

**Advantages:**
- Delivery of drug from osmotic pumps can be designed to follow true zero-order kinetics.
- Drug release is independent of gastric pH and hydrodynamic condition.
- A high degree of in vitro / in vivo correlation can be obtained from osmotic pumps.
- Deliveries may be delayed or pulsed if desired.
- Drug release from osmotic systems is minimally affected by the presence of food.
- They are well characterized and understood.
- Higher release rates are possible with osmotic systems compared with conventional diffusion-controlled drug delivery systems.

**Disadvantages:**
- Special equipment is required for making an orifice in the system.
- Dose dumping.
- Expensive.
- It may cause irritation or ulcer due to release of saturated solution of drug.
- Retrieval therapy is not possible in the case of unexpected adverse events.

**Basic Components of OCDDS**

1. **Drug\(^{(11,21)}\)**
   - Short biological half-life (2-6 hrs)
   - High potency
   - Required for prolonged treatment

2. **Wicking agents\(^{(32)}\)**
   - A wicking agent is defined as a material with the ability to draw water into the porous network of a delivery device.
   - A wicking agent may be swellable or non-swellable in nature.
   - The function of wicking agent is to carry water to surfaces inside the core of the tablet, thereby creating channels or a network of increased surface area.
   - The examples are colloidal silicon dioxide, PVP and sodium lauryl sulphate.

3. **Osmogens\(^{(33)}\)**
   Upon penetration of biological fluid into the osmotic pump through semipermeable membrane, osmogens are dissolved in the biological fluid, which creates osmotic pressure buildup inside the pump and pushes medicament outside the pump through the delivery orifice.
   - Examples are potassium chloride, sodium chloride, and mannitol.
4. **Semipermeable membrane**\(^{(33)}\)

The membrane should possess following characteristics,

- Should be biocompatible
- Sufficient wet strength
- Should be sufficient thick to withstand the pressure within the device
- Rapid and non-swelling

5. **Surfactants**

The surfactants act by regulating the surface energy of materials to improve their blending into the composite and maintain their integrity in the environment of use during the drug release period.

Surfactants such as polyoxyethylenated glyceryl recinoleate, polyoxyethylenated castor oil having ethylene oxide, and glycerol are in corporate into the formulation.

6. **Hydrophilic and hydrophobic polymers**\(^{(20)}\)

These polymers are used for making drug containing matrix core. The selection is based on the solubility of the drug as well as the amount and rate of drug to be released from the pump.

Hydrophilic polymers such as hydroxyl ethylcellulose, carboxy methylcellulose, hydroxyl propyl methyl cellulose, and hydrophobic polymers such as ethyl cellulose and wax materials can be used for this purpose.

7. **Pore forming agents**\(^{(34)}\)

The pore formers should be non-toxic, and on their removal, channels should be formed. The channels should be transport path for fluid.

- **Alkaline metal salts** such as sodium chloride, sodium bromide, potassium chloride potassium sulphate, potassium phosphate etc.,
- **Alkaline earth metals** such as calcium chloride and calcium nitrate,
- **Carbohydrates** such as sucrose, glucose, fructose, mannose, lactose, sorbitol, mannitol, diols, polyvinyl pyrrolidone.

8. **Plasticizers**\(^{(35,36)}\)

Plasticizers or low molecular weight diluents are added to modify the physical properties and improve film forming characteristics of polymers.

Generally from 0.001 to 50 parts of a plasticizer or a mixture of plasticizers are incorporated into 100 parts costing materials.

PEG-600, PEG-200, triacetin(TA), dibutylsebacate, ethylene glycolmono acetate, ethylene glycol, diacetate, and diethyl tartrate used as plasticizer in formulation of semipermeable membrane.
9. Coating solvents

Inert inorganic and organic solvents that do not adversely harm the core, wall and other materials are used as coating solvents. They include methylene chloride, acetone, methanol, ethanol, isopropyl alcohol, butyl alcohol, ethyl acetate, cyclohexane, carbon tetrachloride, water.

Factors affecting drug release rate from osmotic controlled devices

1. Osmotic pressure

Osmotic pressure is one of the most rate controlling factor that must be optimized is the osmotic pressure gradient between inside the compartment and the external environment. The rate of drug release is mainly depends upon the atmospheric pressure created by osmogen. The simplest and most predictable way to achieve a constant osmotic pressure for constant delivery of drug is to maintain a saturated solution of suitable osmotic agent in the compartment. Sometimes combination of osmotic agents is also used for desired osmotic pressure.

2. Membrane thickness

A principle factor controlling the rate of penetration of water into the dispenser is the thickness of the membrane. The permeability of water into the membrane can be enhanced by the choice of a suitable type of the membrane material. The time of release the active constituent can be easily varied by as much as 1000 fold based upon the thickness of the membrane. In general the rate of drug release can be achieved by varying the membrane material. While small change up to a five percent can be best achieve by varying the thickness of the membrane.

3. Delivery orifice

Majority of osmotic delivery systems contain at least one delivery orifice (preformed or formed in situ) in the membrane for drug release.

Size of delivery orifice must be optimized to control the drug release from osmotic system. The size of delivery orifice must be smaller than maximum size $S_{max}$ to minimize drug delivery diffusion through the orifice.

4. Type of membrane and characteristics

Drug release from an osmotic system is largely independent of the pH and agitation intensity of GIT tract. This is because of its selective water permeable membrane and effective isolation of dissolution process of drug core from the gut environment. Among the cellulose polymer cellulose acetate membrane are mostly used because of its high water permeability characteristics and it can be adjusted varying the degree of acetylation of the polymer. The permeability of this membrane can be increased by adding plasticizer to the polymer, which increases the water diffusion coefficient or hydrophilic flux enhancer which increases the water sorption of the membrane.
Classification of osmotically controlled drug delivery system

Oral osmotic drug delivery system

- Single chamber osmotic pump:
  - Elementary osmotic pump

- Multi-chamber osmotic pump:
  - Push pull osmotic pump
  - Osmotic pump with nonexpanding second chamber

Implantable osmotic drug delivery system

- Rose Nelson pump
- Higuchi Leeper pump
- Higuchi Theeuwes pump

Miscellaneous

- Controlled porosity osmotic pump
- Osmotic bursting osmotic pump
- Liquid OROS
- Telescopic Capsule for Delayed Release
- OROS-CT (colon targeting)
- Sandwiched osmotic tablet system

Oral osmotic drug delivery system

Single chamber osmotic pump

Elementary osmotic pump (EOP)\(^{(23,16,18)}\)

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

Push-pull osmotic pump (PPOP) \(^{(23)}\)

Two compartments: upper compartment (drug compartment) contains the drug along with osmotically active agents. Lower compartment (push compartment) contains the polymeric osmotic agents. Mechanism of action of PPOP is when the dosage form comes in contact with the aqueous environment, both compartments imbibe water simultaneously. Because the lower compartment is devoid of any orifice, it expands and pushes the diaphragm into the upper drug chamber, thereby delivering the drug via the delivery orifice. PPOP deliver both highly water-soluble (oxybutynin) and practically water-insoluble (nifedipine, glipizide) drugs.

Limitation

Complicated laser drilling technology should be employed to drill the orifice next to the drug compartment.
Osmotic Pump with Non-Expanding Second Chamber

The second category of multi-chamber devices comprises system containing a non-expanding chamber. This group can be divided into two sub groups depending on the function of second chamber. This type of devices consist of two rigid chamber, the first chamber contains a biologically inert osmotic agent, such as sugar or a simple salt like sodium chloride, the second chamber contains the drug. In use water is drawn into both the chamber through the surrounding semipermeable membrane. The solution of osmotic agent formed in the first chamber then passes through the connecting hole to the drug chamber where it mixes with the drug solution before exiting through the micro porous membrane that form a part of wall surrounding the chamber. The device could be used to deliver relatively insoluble drugs.

Implantable osmotic drug delivery system

Rose-Nelson Pump

Rose and Nelson, the Australian scientists, were initiators of osmotic drug delivery. In 1955, they developed an implantable pump, which consists of three chambers: a drug chamber, a salt chamber contains excess solid salt, and a water chamber. The drug and water chambers are separated by rigid semipermeable membrane. The design and mechanism of this pump is comparable to modern push pull osmotic pump. Disadvantage of this pump was the water chamber, which must be charged before use of the pump.

Higuchi-Leeper Pump

Several simplifications in Rose-Nelson pump were made by Alzacorporation in early 1970s. The Higuchi-Leeper pump is modified version of Rose-Nelson pump. It has no water chamber, and the device is activated by water imbibed from the surrounding environment. 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.

Higuchi-Theeuwes Pump

The pump comprises a rigid, rate controlling outer semipermeable membrane surrounding a solid layer of salt coated on the inside by an elastic diaphragm and on the outside by the membrane. In use, water is osmotically drawn by the salt chamber, forcing drug from the drug chamber. Most of the Higuchi-Theeuwes pumps use a dispersion of solid salt in a suitable carrier for the salt chamber of the device.
Miscellaneous

**Controlled porosity osmotic pump (CPOP)**\(^{(23)}\)

It is an osmotic tablet wherein the delivery orifices (holes) are formed in situ through leaching of water soluble pore-forming agents incorporated in semipermeable membrane (SPM) (e.g., urea, nicotinamide, sorbitol, etc.). Drug release rate from CPOP depends on various factors like coating thickness, solubility of drug in tablet core, level of leachable pore-forming agent(s) and the osmotic pressure difference across the membrane.

![Controlled Porosity Osmotic Pump](image)

**Osmotic Bursting Osmotic Pump**\(^{(23)}\)

This system is similar to EOP except delivery orifice is absent and size may be smaller. When it is placed in an aqueous environment, water is imbibed and hydraulic pressure is built up inside until the wall rupture and the content are released to the environment. Varying the thickness as well as the area the semipermeable membrane can control release of drug. This system is useful to provide pulsated release.

**Liquid Oral Osmotic system (L-OROS)**

Two types: L-OROS Soft cap and L-OROS hard cap. In soft cap, liquid drug formulation is present in a soft gelatin capsule, which surrounded with the barrier layer, the osmotic layer, and the release rate-controlling membrane. In hard cap, it consists of a liquid drug layer and an osmotic engine, all escaped in a hard gelatin capsule and coated with SPM. The expansion of the osmotic layer results in the development of hydrostatic pressure, thereby forcing the liquid formulation to break through the hydrated gelatin capsule shell at the delivery orifice. Water is imbibed across the SPM expanding the osmotic engine, which pushes against the barrier, releasing the drug through the delivery orifice.

**Telescopic capsule for delayed release**\(^{(28,29)}\)

This device consists of two chambers, first one contains the drug and an exit port, and the second contains osmotic engine. Layer of wax-like material separates the two sections. As fluid imbibed
the housing of the dispensing device, the osmotic engine gets expand and exerts pressure on the slidable connected first and second wall sections.

**OROS-CT**\(^{(24)}\)

OROS-CT (Alza corporation) is used as a once or twice a day formulation for targeted delivery of drugs to the colon. It can be a single osmotic agent or comprised of as many as five to six push pull osmotic pump unit filled in a hard gelatin capsule.

**Sandwiched Osmotic Tablet (SOT)**\(^{(24)}\)

In sandwiched osmotic tablet (SOTS), a tablet core consisting of a middle push layer and two attached drug layers is coated with a SPM. As seen in Fig. 10, both the drug layers are connected to the outside environment via two delivery orifices (one on each side). After coming in contact with the aqueous environment, the middle push layer containing swelling agents swell and the drug is released from the delivery orifices. The advantage with this type of system is that the drug is released from two orifices situated on two opposite sides of the tablet thus can be advantageous in case of drugs which are prone to cause local irritation of gastric mucosa.

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**fig: OROS-CT**

**fig: Sandwiched osmotic pump**

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Evaluation parameters for osmotic tablet\(^{[30, 38]}\)

- **Visual inspection:**
  Visual inspection of the film for smoothness, uniformity of coating, edge overage and luster

- **Coating uniformity:**
  The uniformity of coating among the tablets can be estimated by determining the weight, thickness and diameter of the tablet before and after coating

- **Coat weight and thickness:**
  The coat weight and thickness can be determined from depleted devices by following careful washing and drying of the film using standard analytical balance and screw guage.

- **Orifice diameter:**
  The mean orifice diameter of the osmotic pump tablet can be determined by using scanning electron microscopy (SEM)

- **In vitro drug release:\(^{[35]}\)**
  The invitro drug release rate of drug from osmotic system can be determined using diverse methodologies, conventional USP dissolution apparatus I &II.

### Table no 3: Marketed Product

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>API</th>
<th>Type</th>
<th>Marketed by</th>
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<tr>
<td>UT-15C</td>
<td>Treprostinildiethanolamine</td>
<td>SEOP</td>
<td>United therapeutics</td>
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<tr>
<td>LCP-Lerc</td>
<td>Lercanidipine</td>
<td>DOEOP</td>
<td>Osmotica</td>
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<tr>
<td>Cadura CRD</td>
<td>Doxazosinmesylate</td>
<td>PPOP</td>
<td>Alza/Pfizer</td>
</tr>
<tr>
<td>Oxycontin</td>
<td>Oxycodone</td>
<td>PPOP</td>
<td>Alza</td>
</tr>
<tr>
<td>Elafax XR</td>
<td>Valenfexine HCL</td>
<td>EOP</td>
<td>Phoenix</td>
</tr>
<tr>
<td>Invega</td>
<td>Paliperidone</td>
<td>PPOP</td>
<td>Xian-Janssen</td>
</tr>
<tr>
<td>Volmax</td>
<td>Albuterol</td>
<td>EOP</td>
<td>GSK/Muro</td>
</tr>
<tr>
<td>Fortamet</td>
<td>Metformin/pioglitazone</td>
<td>SCOT</td>
<td>Andrax</td>
</tr>
<tr>
<td>Alto plus XR</td>
<td>Metformin</td>
<td>SCOT</td>
<td>Takeda</td>
</tr>
<tr>
<td>Dynacric CR</td>
<td>Isradipine</td>
<td>PPOP</td>
<td>Alza/Novartis</td>
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<tr>
<td>Jusnista</td>
<td>Hydromorphone</td>
<td>PPOP</td>
<td>J&amp;J</td>
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</table>
Brand Name | API | Type | Marketed by
--- | --- | --- | ---
Altoprev | Lovastatin | EOP | Andrex
Allegra D24 h | Fexofenadine | DOEOP | Osmotica
Topamax | Toperamate | PSOP | Alza
Mildugen D | Astemizole | DOEOP | Osmotica
Alpress LP | Prazosin | PPOP | Pfizer
Acutrim | Phenylpropanolamine | EOP | Alza
Glucotrol XL | Glipizide | PPOP | Pfizer
Minipress XL | Prazocin | EOP | Alza

CONCLUSION:

Development efforts of oral osmotic controlled drug delivery systems during recent years have been very dynamic with the emergence of new technologies and products. With the expiration of oral osmotic controlled drug delivery systems primary patents and the increasing demands of health authorities for improved patient treatment compliance and tolerability, the oral osmotic controlled drug delivery systems is primed to increase their market within oral modified-release dosage forms. Nowadays, the large variety of OODS technologies available allows an interesting adaptation of the system to the drug properties and dosage strength. Despite of controversy concerning the safety in the administration of non-disintegrable tablets, the reported clinical benefits have opened up new perspectives to the future development of drugs as oral osmotically driven systems.

REFERENCES:


