Review: Osmotic drug delivery systems current scenario
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ABSTRACT

Osmotic drug delivery systems are new approach for a controlled release dosage form. Various patents available for osmotic drug delivery system like Rose-Nelson pump, Higuchi-Leeper pump, Higuchi-Theeuwes pump, elementary osmotic pump etc. ODDS is useful for poorly soluble drug, for pulsatile drug release, zero order release. Various techniques available for preparation of ODDS include push pull osmotic Pump, osmotic Brusting osmotic pump, liquid oral osmotic system, sandwiched osmotic tablets (SOTS), delayed delivery osmotic device, monolithic osmotic System and controlled porosity osmotic Pump. Osmotically controlled oral drug delivery systems utilize osmotic pressure for controlled delivery of active agent(s). Drug delivery from these systems, to a large extent, is independent of the physiological factors of the gastrointestinal tract. These systems can be utilized for systemic as well as targeted delivery of drugs. By optimizing formulation and processing factors, it is possible to develop osmotic systems to deliver drugs of diverse nature at a pre-programmed rate. In the present review, different types of oral osmotic systems, various aspects governing drug release from these systems, and critical formulation factors are discussed.

Keywords: Osmotic drug delivery system, Zero order release, Pulsatile drug release

INTRODUCTION

The first report of an osmotic effect dates to Abbe Nollet (1748), but Pfeffer obtained the first quantitative measurements in 1877. In Pfeffer’s experiment, a membrane permeable to water but impermeable to sugar is used to separate a sugar solution from pure water. A flow of water then takes place into the sugar solution that cannot be halted until a pressure $p_r$ is applied to the sugar solution. Pfeffer showed that this pressure, the osmotic pressure $\pi$ of the sugar solution, is directly proportional to the solution concentration and the absolute temperature. Within a few years, Van’t Hoff had shown the analogy between these results and the ideal gas laws by the expression

$$p = \theta cRT$$

Where $\theta$ is the osmotic coefficient of the solution (equal to 1 for dilute solutions) and where c is the molar concentration of sugar (or other solute) in the solution, R is the gas constant, and T the absolute temperature.

Osmotic pressures for concentrated solutions of soluble solutes commonly used in controlled release formulations are extremely high, ranging from 30 atm for sodium phosphate up to 500 atm for a lactose-fructose mixture. These osmotic pressures can produce high water flows across semi permeable membranes. The osmotic water flow across a membrane is given by the equation

$$\frac{dV}{dt} = \frac{A(\Delta p)}{L}$$

Where $dV/dt$ is the water flow across the membrane of area A, thickness l, and osmotic permeability $\alpha$ and osmotic pressure difference between the two solutions on either side of the membrane. This equation is only strictly true for completely perm selective membranes: that is, membranes permeable to water but completely impermeable to the osmotic agent. Typical values for the osmotic water permeability of cellulose membranes range from $1 \times 10^{-5}$ to $1 \times 10^{-7}$ cm$^3$/cm$^2$.h.atm.

WHAT IS OSMOSIS?

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

OSMOTIC PUMPSYSTEM

- Rose-Nelson pump
- Higuchi-Leeper pump
- Higuchi-Theeuwes pump
- Elementary osmotic pump

ROSE-NELSON PUMP

Principle of the three-chamber Rose-Nelson osmotic pump first described in 1955. The forerunner of modern osmotic devices was the Rose-Nelson pump$^2$. Rose and Nelson were two Australian physiolo-
gists interested in the delivery of drugs to the gut of sheep and cattle. Their pump was never patented. The pump consisted of three chambers: a drug chamber, a salt chamber containing excess solid salt, and a water chamber. The drug and water chambers are separated by a rigid semi permeable membrane. The difference in osmotic pressure across the membrane moves water from the water 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 chambers, thereby pumping drug out of the device. The pumping rate of the Rose-Nelson pump is given by the Equation

\[
\frac{dM}{dt} = \frac{dV}{dt} \cdot c
\]

Where \( \frac{dM}{dt} \) is the drug release rate, \( \frac{dV}{dt} \) is the volume flow of water into the salt chamber, and \( c \) is the concentration of drug in the drug chamber.

**HIGUCHI-LEEPER PUMP**

The Higuchi-Leeper pump\(^3\) was modified series of Rose-Nelson pump. It has no water chamber, and the device is activated by water imbibed from the surrounding environment. This means the pump can be prepared loaded with drug and then stored for weeks or months prior to use. The pump is activated when it is swallowed or implanted in the body. Higuchi-Leeper pumps contain a rigid housing, and the semi permeable membrane is supported on a perforated frame.\(^4,5\) This type of pump usually has a salt chamber containing a fluid solution with excess solid salt. Most recent system in this series used for pulsatile drug delivery system.

**HIGUCHI-THEEUWES PUMP**

In the early 1970s, Higuchi and Theeuwes\(^6\) developed another, even simpler variant of the Rose-Nelson pump. As with the Higuchi-Leeper pump, water to activate the osmotic action of the pump is obtained from the surrounding environment. In the Higuchi-Theeuwes device, however, the rigid housing is dispensed with and the membrane acts as the outer casing of the pump. This membrane is quite sturdy and is strong enough to withstand the pumping pressure developed inside the device. The device is loaded with the desired drug prior to use. When the device is placed in an aqueous environment, release of the drug follows a time course set by the salt used in the salt chamber and the permeability of the outer membrane casing. Most of the Higuchi-Theeuwes pumps use a dispersion of solid salt in a suitable carrier for the salt chamber of the device.

**ELEMENTARY OSMOTIC PUMP**

The seminal invention that made osmotic delivery a major method of achieving controlled drug release was that of the elementary osmotic pump by Theeuwes\(^7\) in 1974. The device is a further simplification of the Higuchi-Theeuwes pump, and eliminates the separate salt chamber by using the drug itself as the osmotic agent. The device is formed by compressing a drug having a suitable osmotic pressure into a tablet using a tableting machine. The tablet is then coated with a semi permeable membrane, usually cellulose acetate, and a small hole is drilled through the membrane coating.

**OSMOTIC FORMULATION SYSTEM**

- Push Pull Osmotic Pump
- Osmotic Brusting Osmotic Pump
- Liquid Oral Osmotic System
- Sandwiched Osmotic Tablets (SOTS)
- Delayed Delivery Osmotic Device
- Monolithic Osmotic System
- Controlled Porosity Osmotic Pump

**PUSH PULL OSMOTIC PUMP**

Push pull osmotic systems (PPOS), also known as push-pull osmotic pumps, have been successfully developed and marketed to extend the release of poorly soluble compounds for various indications, such as hypertension, diabetes, and asthma. In these chronic disease treatments, PPOS were reported as a drug delivery technology reducing the food interaction often observed with poorly soluble drug substances\(^8\) as well as enabling a once-a-day administration and thereby patient compliance\(^9\).

Push Pull Osmotic Pump is possible to deliver both poorly water-soluble and highly water soluble drugs at a constant rate. One layer (depict as the 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. When the system is placed in aqueous environment water is attracted into the tablet by an osmotic agent in both the layers. The osmotic attraction in the drug layer pulls water into the compartment to form in situ a suspension of drug. The osmotic agent in the non-drug layer simultaneously attract water into that compartment, causing it to expand volumetrically and the expansion of non drug layer pushes the drug suspension out of the delivery orifice.

**OSMOTIC BRUSTING OSMOTIC PUMP**

In this system 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\(^10\). Varying the thickness as well as the
area the semi permeable membrane can control release of drug. This system is useful to provide pulsed release.

**LIQUID ORAL OSMOTIC SYSTEM**

These systems include a liquid drug layer, an osmotic engine or push layer and a semi permeable membrane coating. When the system is in contact with the aqueous environment water permeates across the rate controlling membrane and activate the osmotic layer. The expansion of the osmotic layer results in the development of hydrostatic pressure inside the system, thereby forcing the liquid formulation to be delivered from the delivery orifice. Where as LOROS hard cap or soft cap systems are designed to provide continuous drug delivery, the LOROS delayed liquid bolus drug delivery system is designed to deliver a pulse of liquid drug. The delayed liquid bolus delivery system comprises three layers: a placebo delay layer, a liquid drug layer and an osmotic engine, all surrounded by rate controlling semi permeable membrane. The delivery orifice is drilled on the placebo layer end of the capsule shaped device. When the osmotic engine is expands, the placebo is released first, delaying release of the drug layer. Drug release can be delayed from 1 to 10 hour, depending on the permeability of the rate controlling membrane and thickness of the placebo layer.

**SANDWICHED OSMOTIC TABLETS (SOTS)**

It is composed of polymeric push layer sandwiched between two drug layers with two delivery orifices. When placed in the aqueous environment the middle push layer containing the swelling agents swells and the 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.

**DELAYED DELIVERY OSMOTIC DEVICE**

This device consists of two chambers, the first contains the drug and an exit port, and the second contains an osmotic engine. A layer of wax like material separates the two section. To assemble the delivery device, the desired active agent is placed into one of the sections by manual or automated fill mechanism. The bilayer tablet with the osmotic engine is placed into a completed cap part of the capsule with the convex osmotic layer pointed in to the closed end of the cap and the barrier into the closed end of the cap and the barrier layer exposed towards the cap opening. The open end of the filled vessel is fitted inside the open end of the cap, and the two pieces are compressed together until the cap, osmotic bilayer tablet and vessel fit together tightly. As fluid is imbibed the housing of the dispensing device, the osmotic engine expand and exerts pressure on the slidable connected first and second wall sections. During the delay period the volume of reservoir containing the active agent is kept constant, therefore a negligible pressure gradient exists between the environment of use and interior of the reservoir. As a result, the net flow of environmental fluid driven by the pressure enter the reservoir is minimal and consequently no agent is delivered for the period.

**MONOLITHIC OSMOTIC SYSTEM**

It constitutes a simple dispersion of water-soluble agent in polymer matrix. When the system comes in contact in with the aqueous environment. Water imbibition by the active agents 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 then matrix in a serial fashion. However this system fails if more then 20–30 volumes per liter of the active agents are incorporated in to the device as above this level, significant contribution from the simple leaching of the substance take place.

**CONTROLLED POROSITY OSMOTIC PUMP**

The pump can be made with single or multicompartmemt dosage form, in either form, the delivery system comprises a core with the drug surrounded by a membrane which has an asymmetric structure, i.e. comprises a thin dense skin layer supported by a porous substructure. The membrane is formed by phase inversion process controlled by the evaporation of a mixed solvent system. Membrane is permeable to water but impermeable to solute and insensitive pore forming additive dispersed through out the wall.

**EVALUATION PARAMETER OF OSMOTIC DRUG DELIVERY FORMULATION**

- Characterization of dosage form
- Effect of osmotic agents
- Swelling properties
- Membrane stability and thickness
- Orifice diameter and drug release
- In-vitro drug release study

**OSMAT**

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 thus judiciously combines both matrix osmotic
characteristics 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 represents simple, versatile, and easy to fabricate osmotically driven controlled drug delivery system based upon low cost technology.

**OSMATPUMP**

The pump can be made with single or multicompartment dosage form, in either form, the delivery system comprises a core with the drug surrounded by a membrane which has an asymmetric structure, i.e. comprises a thin dense skin layer supported by a porous substructure. The membrane is formed by phase inversion process controlled by the evaporation of a mixed solvent system. Membrane is permeable to water but impermeable to solute and insensitive pore forming additive dispersed through out the wall\[18]. When exposed to water, low levels of water-soluble additive are leached from polymer materials that were permeable to water yet remained insoluble. Then resulting sponge like structure formed the controlled porosity walls of interest and was substantially permeable to both water and dissolved drug agents. Rate of drug delivery depends upon the factors are water permeability of the semi permeable membrane and the osmotic pressure of the core formulation, thickness and total surface area of coating. All of these variable are under the control of the designer and do not vary under physiological condition, leading to the robust performance alluded to above. The rate of flow dv/dt of water into the device can be represented as

\[
\frac{dv}{dt} = \frac{Ak}{h} (D_p - DR)
\]

Where, 
A = Area of the membrane
k = Membrane permeability
Dp = Difference in osmotic pressure
DR = Hydrostatic pressure difference

**ASYMMETRIC MEMBRANE DOSAGE FORMS**

Drug delivery from asymmetric membrane dosage forms is primarily controlled by the difference in osmotic pressure between the external fluid and drug-containing core of the dosage form. The mechanism of drug release from an AM tablet consists of imbibitions of water through the membrane into the tablet core, dissolution of soluble components (including drug) in the core, and pumping of the solution out of pores in the membrane. The imbibitions of water through the membrane are driven by its thermodynamic activity gradient between the external medium, e.g., receptor solution or gastric / intestinal fluids, and the osmotic agent(s) in the core. Dissolution of the solute components within the core produces the activity gradient and establishes the osmotic pressure difference between the core and external environment. The approximately constant dosage form volume means that the volume of drug solution delivered will be roughly equal to the volume of water imibed within a given time interval. As water diffuses into the core, the volume of the imbibed water creates a hydrostatic pressure difference across the membrane, which forces the solution out through the pores in the coating. Therefore, the rate of drug delivery will be constant as long as a constant osmotic pressure gradient is maintained across the membrane, the membrane permeability remains constant, and the concentration of drug in the expelled solution is constant. Sustained zero-order drug release can be achieved using AM devices while the concentration of dissolved drug within the fluid portion of the core remains constant. When the drug concentration in the core fluid falls below saturation, the release rate declines.

**ADVANTAGE OF ASYMMETRIC MEMBRANE DOSAGE FORM**

1. Higher water flux and permeability of symmetric membranes allows greater flexibility in designing faster release rates or incorporating lower solubility drug substances into the dosage form
2. The skin layer porosity is easily controlled with selection of pore former type and concentration.
3. The ability to fabricate AM dosage forms in conventional pharmaceutical process equipment without additional manufacturing complexities.

**EVALUATION PARAMETER OF ASYMMETRIC MEMBRANE DOSAGE FORM**

- Colour
- Any imperfection
- Texture and membrane size
- Size Height and radius
- Scanning electron microscopy
- Drug content
- Dissolution behavior
- Stability studies

**VARIOUS DRUG AVAILABLE IN MARKET WITH OSMOTIC DRUG DELIVERY SYSTEM**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Osmotic agent</th>
<th>Polymer osmogents</th>
<th>Formulation</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irsadipine</td>
<td>Magnesium sulphate</td>
<td>Sodium carboxymethyl cellulose</td>
<td>Push - Pull</td>
<td>5, 10 mg</td>
</tr>
<tr>
<td>Pseudoephiderine</td>
<td>Sodium chloride</td>
<td>Hydroxypropylmethyl cellulose</td>
<td>Elementary Pump</td>
<td>60 mg IR, 180 mg CR</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>Sodium bicarbonate</td>
<td>Hydroxyethylmethyl cellulose</td>
<td>Sandwiched Osmotic Tablets</td>
<td>10, 20 mg</td>
</tr>
<tr>
<td>Chlorpheniramine</td>
<td>Sodium sulphate</td>
<td>Methylcellulose</td>
<td>Elementary Pump</td>
<td>4 mg IR, 12 mg CR</td>
</tr>
<tr>
<td>Glipizide</td>
<td>Potassium chloride</td>
<td>Polyethylene oxide</td>
<td>Push - Pull</td>
<td>5, 10 mg</td>
</tr>
<tr>
<td>Verapamil</td>
<td>Potassium chloride</td>
<td>Polyvinyl pyrollidine</td>
<td>Push - Pull with time delay</td>
<td>180, 240 mg</td>
</tr>
<tr>
<td>Pheynylpropranolamine</td>
<td>Sodium chloride</td>
<td>Polyethylene oxide</td>
<td>Elementary pump</td>
<td>75 mg</td>
</tr>
<tr>
<td>Praozosin</td>
<td>Potassium chloride</td>
<td>Hydroxypropylmethyl cellulose</td>
<td>Push - Pull</td>
<td>2.5 - 5 mg</td>
</tr>
</tbody>
</table>

**REFERENCE:**


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