OSMOTIC PUMP: A NOVEL APPROACH TO CONTROL DRUG DELIVERY

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ABSTRACT

Controlled release dosage forms are designed to complement the pharmaceutical activity of the medicament in order to achieve constant plasma level over a longer time period. Among various approaches of drug delivery, osmotically controlled drug delivery system is one of the promising technologies. It is one of the novel drug delivery system which can control release of drug from the dosage form. It provides a better control of plasma drug level which helps in increased efficacy and constant delivery. These systems utilize osmotic pressure as major driving force for delivery of drug. Osmotic pump consists of inner core consists of drug and osmogen. This inner core coated with a semi-permeable membrane. When this system exposed to gastrointestinal fluids, water flows through the semi-permeable membrane into the system due to osmotic pressure difference which dissolves the drug and pumps it out through the orifice by the osmotic force. Drug release from the osmotic pump in a controlled manner which is independent of chemical properties of the drug, patient’s physiological factors or concomitant food intake; this is the primary advantage of osmotic drug delivery system. In this article, various types of osmotic pump, the basic components of osmotic pump and evaluation of osmotic tablets have been discussed briefly.

Keywords
Osmotic Drug Delivery System,
Osmotic Pressure,
Osmogen,
Semi-Permeable Membrane.

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INTRODUCTION

A number of newer drug delivery systems are under investigation to get rid of the limitations commonly found in conventional dosage form and improve therapeutic efficacy of the respective drug [1]. Drug with short half-life need frequent administration if formulated as conventional dosage form. In conventional dosage form fluctuations in drug concentration may lead to under medication or over medication. In case of over medication of drug with small therapeutic index precipitation of adverse effects may occur. Further rate and extend of drug release from conventional formulations depends on properties of drug, physiological properties of GI tract. To overcome these limitations of conventional dosage form, drugs can be release from oral osmotic pump (OROS) in a controlled manner for a longer time period, by the technique of osmosis [2, 9].

Osmosis:

Osmosis is spontaneous net movement of solvent molecules through a semi-permeable membrane from a region of low solute concentration to a region of higher solute concentration, until equalize solute concentration on each side. It occurs without applying any external energy.

Osmosis is follows passive transport mechanism. In osmosis water diffuses from a hypotonic solution to a hypertonic solution i.e low concentration to higher concentration. Generally speaking, the direction of water flow is determined by the solute concentration and not by the “nature” of the solute molecule themselves.

Osmotic pressure is a colligative property, which depends on concentration of solute that contributes to osmotic pressure [3]. Delivery of drug from osmotic pump depends on difference between osmotic pressure of inside and outside environment of osmotic pump. At biological environment, water diffuses into osmotically controlled drug delivery system through semi-permeable membrane and dissolves a fraction of drug. This builds up concentration or osmotic gradient between inner environment and biological fluid. It permits drug diffusion from higher concentration to lower concentration. When water enters osmotic system it forms an internal hydrostatic pressure that pumps drug solution out of the device [4]. The rate of drug delivery from osmotic pump is directly proportional to the osmotic pressure developed due to imbibitions of fluids by osmogen [5]. Drug release from this system does not depend on physiological factors of the gut lumen, and the release characteristics can be predicted easily from the known properties of the drug and dosage form. Drug release from this system is independent of pH and other physiological parameters to large extent and it is possible to modulate the release characteristic by optimizing the properties of the drug and system [3].

Fig. 1: Oral osmotic pump

Osmotic pump tablets generally consists of an inner core consists of drug and an osmotically active agent or osmogen like potassium chloride or mannitol, surrounded by a rigid semi-permeable membrane [3, 6]. By the help of different techniques like mechanical drill, laser beam etc an orifice is created on semi-permeable membrane through which drug can diffuse to outer environment [2].

Drug release from oral osmotic pumps follows zero order kinetics [2] i.e. release from the dosage form is independent of gastric pH and hydrodynamic conditions of these osmotically controlled drug delivery system [7].

Advantages

The following advantages have contributed to the popularity of osmotic drug delivery systems [8-10].

- Frequency of dosing is reduced and patient compliance is improved.
- Sustained and consistent blood levels within the therapeutic window can be achieved.
- The delivery rate of zero order is achievable with osmotic system.
- Drug delivery may be delayed or pulsed, if required.
- The release from osmotic system is minimal affected by presence of food in gastrointestinal tract.

Disadvantages

- It is expensive to formulate the dosage form.
- Dose dumping may occur if coating is not done properly.
- Size of hole is critical parameter which may control drug release from the dosage form.

Present review is an update on basic components of osmptic pump and evaluation requirements for osmotic systems.
GENERAL MECHANISM FOR DRUG RELEASE FROM OSMOTIC PUMPS

As described earlier, the basic equation which applies to osmotic system is
\[ \frac{dM}{dt} = \frac{dV}{dt} \cdot c \]  
...............(eq1)

Where, \( \frac{dM}{dt} \) = mass release,  
\( \frac{dV}{dt} \) = volumetric pumping rate and  
c = concentration of drug

But,
\[ \frac{dV}{dt} = \left( \frac{A}{h} \right) \cdot L_p \cdot (\sigma \Delta \pi - \Delta p) \]

Where, A= membrane area,  
h= thickness of membrane,  
\( L_p \)= mechanical permeability,  
\( \sigma \)= reflection coefficient,  
\( \Delta \pi \)=osmotic pressure difference,  
\( \Delta p \)= hydrostatic pressure difference.

As the size of orifice delivery increases, \( \Delta p \) decrease, so \( \Delta \pi \gg \Delta p \) and equation becomes
\[ \frac{dV}{dt} = \left( \frac{A}{h} \right) \cdot L_p \cdot (\sigma \Delta \pi) \]

When osmotic pressure of the formulation is large compared to the osmotic pressure of the environment, \( p \) can be substituted for \( \Delta p \),
\[ \frac{dV}{dt} = \left( \frac{A}{h} \right) \cdot L_p \cdot (\sigma \pi) = \frac{A}{hk\pi} \]
\( (k = L_p \sigma = \text{ membrane permeability}) \)

Now, equation 1 can be given as
\[ \frac{dM}{dt} = \left( \frac{A}{h} \right) \cdot k \pi c = \left( \frac{A}{h} \right) \cdot k \pi S \]
\( (S= \text{ solubility of drug, } c \text{ taken as } S) \)

CLASSIFICATION OF OSMOTIC DRUG DELIVERY SYSTEM

Oral osmotic drug delivery systems are principally classified as follows [11, 12] (Fig.2):-

![Diagram of Osmotic Drug Delivery Systems]

- Implantable Systems
  - The Rose and Nelson pump
  - Higuchi Leeper pump
  - Higuchi Theuwes pump
  - Implantable Mini osmotic pump

- Oral System

- Single Chamber Osmotic Pump
  - Elementary osmotic pump

- Multi Chamber Osmotic Pump
  - Push pull osmotic pump
  - Osmotic pump with non-expanding second chamber

- Modified Osmotic Pump
  - Controlled porosity
  - Osmotic bursting osmotic pump
  - Liquid OROS
  - Delayed delivery osmotic device
  - Telescoping capsules
  - Oros CT (Colon targeting)
  - Sandwiched oral therapeutic system
  - Osmotic pump for insoluble drugs

BASIC COMPONENTS USED IN FORMULATION OF OSMOTICALLY CONTROLLED DRUG DELIVERY SYSTEM [13]

Various components that constitute osmotic drug delivery system are as follows:

- Drugs
- Osmotic agents
- Semi-permeable membrane
- Wicking agents
- Solubilizing agents
- Hydrophilic and hydrophobic polymers

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Drugs

Potent drugs with short biological half-life and used for prolonged treatment are ideal candidates for osmotic systems, e.g. Nifedipine, Verapamil etc.

Osmotic agents

Osmotic agents or osmogents maintain an osmotic gradient across the membrane. They also generate a driving force for uptake of water and assist in maintaining drug uniformity in the hydrated formulation. Osmogents may be of inorganic or organic in nature. A water soluble drug may act as an osmogen. 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 [14].

Inorganic water-soluble osmogents: e.g. Sodium chloride, Sodium sulphate, Potassium sulphate, Potassium chloride etc.

Organic polymer osmogents: e.g. Sodium carboxy methyl cellulose, Hydroxy propyl methyl cellulose, Hydroxy ethyl methyl cellulose, Methyl cellulose, Polyethylene oxide, Polyvinyl pyrrolidine.

Semi permeable membrane

Semi-permeable membrane is an important part of the osmotic drug delivery system as it controls water influx into the inside environment of the system. It should be rigid enough to retain its dimensional integrity throughout its operational life time. The semi permeable wall of the elementary osmotic delivery system is composed of a polymeric material cast or sprayed onto the tablet to give a 2-15% coating weight [15]. The membrane should impermeable to solute while allow water permeation to the core of the tablet. The membrane should be inert and maintain its dimensional integrity to provide a constant osmotic driving force during drug delivery. Any polymer that is permeable to water but impermeable to solute can be used as a coating material in osmotic devices e.g. cellulose esters like cellulose acetate, cellulose diacetate, cellulose acetate butyrate, cellulose triacetate, ethyl cellulose etc. [16].

The semi-permeable wall of the tablet can contain at least one passageway communicating the contents of the core with the exterior of the device, delivering the therapeutically active drug through the passageway from the osmotic drug delivery system. The size of an individual passageway can range from 100 microns to 1000 microns, more preferred 300 to 900 microns, and most preferred 500 to 850 microns. One or multiple passageways can be present to communicate the contents with the exterior of the tablet [15].

Ideal properties of semi-permeable membrane:

- The semi-permeable membrane must meet some performance criteria [17]. They are as follows:
  - The material must possess sufficient wet strength (-105) and wet modulus so as to retain its dimensional integrity during the operational lifetime of the device.
  - The membrane exhibit sufficient water permeability so as to retain flux rate in the desired range. The water vapour transmission rates can be used to estimate water flux rates.
  - The reflection coefficient and leakiness of the osmotic agent should approach the limiting value of unity. Unfortunately, polymer membranes that are more permeable to water are also, in general more permeable to the osmotic agent.
  - They should also be biocompatible.
  - Rigid and non-swelling.
  - Should be sufficient thick to withstand the pressure within the device.

Wicking agents

Wicking agents are capable of draw water into the porous network of a delivery system thereby creating channels or a network of an increased surface area. These agents can do this with or without swelling. This may include in the core of this type of tablet formulation. Some materials can both wick water and swell, others can function as wicking agents only. Wicking agents creates channels or pores in the core of the tablet. This facilitates the channeling of water molecules, can loosely adhere to the surfaces of the wicking agent via Vander wall’s interaction between the surface of the wicking agent and absorbed molecule [15].

Materials like colloidal silicon dioxide, kaolin, titanium dioxide, fumed silicon dioxide, alumina, sodium lauryl sulfate, low molecular weight polyvinyl pyrrolidone, m-pyrol, bentoninte, magnesium aluminium silicate, polyester, polyethylene etc may be used as wicking agents.

Solubilizing agents [18]

Solubilizing agents are classified into three groups.

- An agent that inhibits crystal formation of the drugs or otherwise act by complexation with the drug (e.g. PVP, PEG, cyclodextrine).
- A high HLB micelle forming surfactant, particularly anionic surfactant (e.g. Tween 20, 60, 80, poly oxy ethylene or polyethylene containing surfactant and other long chain anionic surfactants such as SLS).
- Citrate esters and their combinations with anionic surfactants (e.g., alkyl esters particularly triethyl citrate).
Hydrophilic and hydrophobic polymers

Along with API polymers are used in formulation of matrix core of osmotic pump. Polymers are chosen according to the nature of the drug to be used. Drugs which are water soluble can be co-entrapped with hydrophobic polymers and drugs which are water insoluble can be co-entrapped with hydrophilic matrices to obtain more controlled release [18]. Generally, mixtures of both hydrophilic and hydrophobic polymers have been used in the development of osmotic delivery system [19]. 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. The polymers are of either swellable or nonswellable nature. Mostly, swellable polymers are used for the pumps contain moderately water-soluble drugs, since they increase the hydrostatic pressure inside the pump due to their swelling nature. The nonswellable polymers are used in case of highly water-soluble drugs [20]. Ionic hydrogels such as sodium carboxy methyl cellulose are preferably used because of their osmogenic nature. More precise controlled release of drugs can be achieved by incorporating these polymers into the formulations. Hydrophilic polymers such as hydroxyl ethyl cellulose, carboxy methyl cellulose, hydroxyl propyl methyl cellulose, high-molecular-weight poly (vinyl pyrrolidone), and hydrophobic polymers such as ethyl cellulose and wax materials can be used for this purpose [21].

Plasticizers

Plasticizers are added to pharmaceutical formulations to modify the physical properties and improve film forming characteristics of polymers. Plasticizers increase the flexibility, durability and stability of the semi permeable membrane. Various types of plasticizers may be single or in combinations are used in coating membrane. These agents play a significant role in the formulations of osmotic systems. The permeability of polymeric film may be affected due to the changes in visco-elastic behavior of polymers by plasticizers [22]. Some of the plasticizers widely used in pharmaceutical formulations are polyethylene glycols, ethylene glycols, triethyl citrates, myristates etc.

Coating solvents

Coating solvent is required to dissolve or disperse the polymer and other additive and convey them to substrate surface. Solvent used to prepare polymeric solution include inert inorganic and organic solvents that do not adversely harm the core, wall and other materials [23]. Methylene chloride, methanol, isopropyl alcohol, cyclohexane, carbon tetrachloride, water etc. can be used alone or in combination as coating solvents.

Flux regulators

Flux regulating agents may be incorporated in the layer to regulate permeability of the fluid. Hydrophilic substances such as polyethylene glycols (300 to 6000 Da), polyhydric alcohols, polyalkene glycols etc helps to improve the flux, whereas hydrophobic materials such as phthalates substituted with an alkyl or alkoxy (e.g., diethyl phthalates or dimethoxyethyl phthalates) tend to decrease the flux. Insoluble salts or insoluble oxides, which are substantially water – impermeable materials, can also be used for this purpose [23].

Pore forming agents

The agents when come in contact with water leach out to form controlled porosity or multiparticulate osmotic pumps. The pore formers can be inorganic or organic and solid or liquid in nature: for example, alkaline metal salts such as sodium chloride, sodium bromide, potassium chloride, potassium sulphate, potassium phosphate etc., alkaline earth metals such as calcium chloride and canitrate, carbohydrates such as sucrose, glucose, fructose, mannose, lactose, sorbitol, mannitol, and diols and polyols such as poly hydroalcohols and polyvinyl pyrrolidone can be used as pore forming agents [23, 24].

EVALUATION OF ORAL OSMOTIC DRUG DELIVERY SYSTEMS

Oral osmotic drug delivery systems can be evaluated using a range of studies [25 - 27]. The designed oral osmotic drug delivery system mainly osmotic pump tablets can be evaluated by:

Visual inspection

Visual inspection of the film is required to know smoothness, uniformity of coating, edge coverage 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 the coating.

Coat weight and thickness

The coat weight and thickness can be determined from depleted devices following careful washing a drying of the film, using standard analytical balance and screw gauge, respectively.

Orifice diameter

The mean orifice diameter of osmotic pump tablet can be determined microscopically using pre-calibrated ocular micrometer.
In vitro drug release

The in vitro delivery rate of drugs from osmotic systems can be determined using diverse methodologies, including vertical reciprocating shaker, conventional USP dissolution apparatus I and II, flow through apparatus, etc. The dissolution medium is generally distilled water as well as simulated gastric fluid (for 2-4 hrs) and intestinal fluids for subsequent hours have been used [28].

In vivo evaluation

As the environment in the intestinal tract of the dog is quite similar to that of human beings in terms of pH and motility, dogs have widely been used for in vivo delivery rate measurement of drug(s) from oral osmotic drug delivery systems and also to establish in vitro/in vivo correlation (IVIVC). In vivo evaluation can also be performed in healthy human volunteers [29].

MARKETED OSMOTIC PUMPS [30, 31]

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>API</th>
<th>Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effidac 24</td>
<td>Chlorpheniramine</td>
<td>Elementary osmotic pump</td>
</tr>
<tr>
<td>Acurrim</td>
<td>Phenylpropanolamine</td>
<td>Elementary osmotic pump</td>
</tr>
<tr>
<td>Minipress XL</td>
<td>Prozasin</td>
<td>Elementary osmotic pump</td>
</tr>
<tr>
<td>Procardia XL</td>
<td>Nifedepine</td>
<td>Push-pull osmotic pump</td>
</tr>
<tr>
<td>Alpress LP</td>
<td>Prazosin</td>
<td>Push-pull osmotic pump</td>
</tr>
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<td>Cardura XL</td>
<td>Doxazosine</td>
<td>Push-pull osmotic pump</td>
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<tr>
<td>Glucotrol</td>
<td>Glipizide</td>
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</tr>
<tr>
<td>Covera HS</td>
<td>Verapamil HCl</td>
<td>Push-pull osmotic pump</td>
</tr>
<tr>
<td>Chronogesic</td>
<td>Sufentanil</td>
<td>Implantable osmotic pump</td>
</tr>
<tr>
<td>Viadur</td>
<td>Leuprolide acetate</td>
<td>Implantable osmotic pump</td>
</tr>
</tbody>
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CONCLUSION

Osmotic pumps are used for controlled delivery of active agent over a longer time period. Osmotic pump generally contains drug core with osmogen coated with a semi-permeable membrane. This semi-permeable membrane may have one or more delivery orifice. Driving force for drug delivery from osmotic pump is osmotic pressure. This system is a novel approach to deliver drug in a constant rate at zero order release kinetics. This system does not depend upon gastric pH and hydrodynamic condition of gastrointestinal tract for release of drug. Osmotic pumps are one among excellent pharmaceutical dosage forms for controlled delivery of drug through oral route.

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