

Overview of Past and Current Osmotic Drug Delivery Systems

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ABSTRACT

In recent years, considerable attention has been focused on the development of novel drug delivery systems (NDDS). Osmotically controlled drug delivery systems (ODDS) are a type of NDDS which utilize osmotic pressure for controlled delivery of active agent(s). The release of drug(s) from osmotic systems is independent of gastric pH & gastric motility. The release of drug(s) from osmotic systems is affected by various formulation factors such as osmotic pressure of the core component(s), solubility and size of the delivery orifice, and nature of semi permeable membrane. Different types of osmotic systems have been developed implantable & oral. This review focuses on types of ODDS and factors affecting release of drug and various formulation factors from the systems.

Keywords: Osmosis, Osmotic drug delivery systems, zero order release, formulation factors.

INTRODUCTION¹

For many decades treatment of an acute disease or a chronic illness has been mostly accomplished by delivery of drugs to patients using various pharmaceutical dosage forms. Traditionally, the oral drug delivery has been popular as the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drugs. Conventional oral drug delivery systems are known to provide an immediate release of drug, in which one 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 factors 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 limitation of oral route is replied by parenteral route. This route offers the advantage of reduced dose, targeting of site and avoiding GI stability, hepatic by-pass of drug molecule.

Osmosis

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. It is driven by a difference in solute concentrations across the membrane that allows passage of water, but rejects most solute molecules or ions. Osmotic pressure is the pressure which, if applied to the more concentrated solution, would prevent transport of water across the

semipermeable membrane². The first osmotic effect was reported by Abbe Nollet in 1748^{3,4}. Later in 1877, Pfeiffer performed an experiment using semi-permeable membrane to separate sugar solution from pure water^{3,4}. He showed that the osmotic pressure of the sugar solution is directly proportional to the solution concentration and the absolute temperature. In 1886, Vant Hoff identified an underlying proportionality between osmotic pressure, concentration and temperature⁴. He revealed that osmotic pressure is proportional to concentration and temperature and the relationship can be described by following equation.

$$\Pi = \varnothing c RT$$

Where, \varnothing = Osmotic pressure, Π = osmotic coefficient, c = molar concentration, R = gas constant, T = Absolute temperature

Osmotically controlled drug delivery systems

Osmotic pressure is used as driving force for osmotic drug delivery system to release the drug in controlled manner. Osmotic drug delivery technique is the most interesting and widely acceptable among all other technologies used for the same. Intensive research has been carried out on osmotic systems and several patents are also published. Development of osmotic drug delivery systems was pioneered by Alza and it holds major number of the patents analyzed and also markets several products based on osmotic principle. These systems can be used for both route of administration i.e. oral and parenteral. Oral osmotic systems are known

as gastro-intestinal therapeutic systems (GITS). Parenteral osmotic drug delivery includes implantable pumps.

Historical aspects of osmotic pumps

About 75 years after discovery of the osmosis principle, it was first used in the design of drug delivery systems. Rose and Nelson, the Australian scientists, were initiators of osmotic drug delivery. In 1955, they developed an implantable pump, which consisted 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 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 design and mechanism of this pump is comparable to modern push-pull osmotic pump. The major disadvantage of this pump was the water chamber, which must be charged before use of the pump⁴.

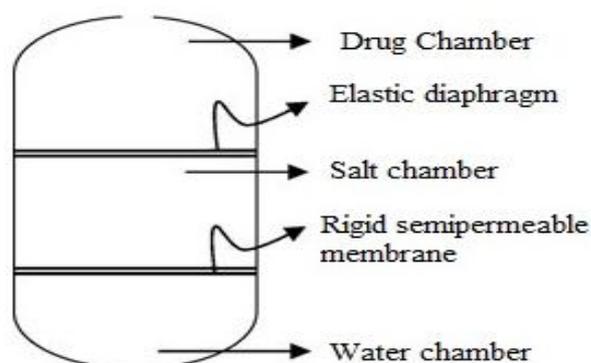


Fig. 1: Rose-Nelson pump

Several simplifications in Rose-Nelson pump were made by Alza Corporation 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 body⁵. 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. Recent modification in Higuchi-Leeper pump accommodated pulsatile drug delivery. The pulsatile release was achieved by the production of a critical pressure at which the delivery orifice opens and releases the drug.

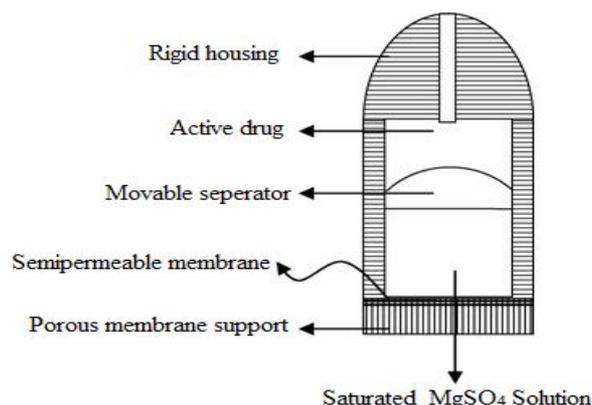


Fig. 2: Higuchi-Leeper pump

Further simplified variant of Rose-Nelson pump was developed by Higuchi and Theeuwes. This 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 chamber³.

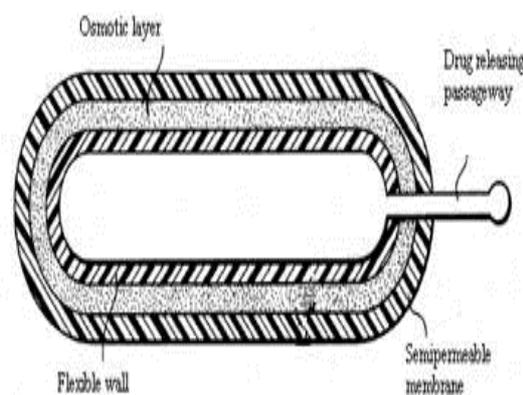


Fig. 3: Higuchi-Theeuwes pump

In 1975, the major leap in osmotic delivery occurred as the elementary osmotic pump for oral delivery of drugs was introduced. The pump consists of an osmotic core containing the drug, surrounded by a semipermeable membrane with a delivery orifice. When this pump is exposed to water, the core imbibes water osmotically at a controlled rate, determined by the membrane permeability to water and by the osmotic pressure of the core formulation. As the membrane is non-expandable, the increase in volume caused by the imbibition of water leads to the development of hydrostatic pressure inside the tablet. This pressure is relieved by the flow of saturated solution out of the device through the delivery orifice. This process continues at a constant rate until the entire solid agent inside the tablet has been dissolved and only a solution filled coating membrane is left. These

residual dissolved agents continue to be delivered at a declining rate until the osmotic pressure inside and outside the tablet are equal⁴.

Basic Component of Osmotic Pumps Drugs

Drug should be Short biological half-life {2-6h}, Highly potent drug, Required for prolonged treatment E.g. nifedipine, glipizide, virapamil, diltizem

Osmotic agents

Osmotic components usually are ionic compounds consisting of either inorganic salts or hydrophilic polymers. These materials maintain a concentration gradient across the membrane.

They also generate a driving force for the uptake of water and assist in maintaining drug uniformity in the hydrated formulation.

Table 1: classification of osmogens

| Osmogens | Example |
|----------------------------------|--|
| Inorganic water-soluble osmogens | Magnesium sulphate, Sodium chloride, Sodium sulphate, Potassium chloride, Sodium bicarbonate |
| Organic polymer osmogens | Sodiumcarboxymethylcellulose, Hydroxypropylmethyl cellulose, Hydroxyethylmethylcellulose, Methylcellulose, Polyethylene oxide, polyvinyl pyrrolidone |
| Carbohydrates | Arabinose, ribose, xylose, glucose, fructose, galactose, mannose, sucrose, maltose, lactose, raffinose, etc. |
| Water-soluble amino acids | Glycine, leucine, alanine, methionine, etc. |

Semi permeable membrane

A semipermeable membrane, also termed a selectively-permeable membrane, a partially-permeable membrane or a differentially-permeable membrane, is a membrane that will allow certain molecules or ions to pass through it by diffusion and occasionally specialized "facilitated diffusion".

An example of a semi-permeable membrane is the lipid bilayer, on which is based the plasma membrane that surrounds all biological cells. Many natural and synthetic materials thicker than a membrane are also semipermeable. One example of this is the thin film on the inside of an egg.

Another example of a semipermeable membrane which is very specific in its permeability is a phospholipid bilayer, a group of phospholipids (consisting of a phosphate head and two fatty acid tails) arranged into a double-layer. The hydrophilic phosphate heads are in the outside layer and exposed to the water content outside and within the cell. The hydrophobic tails are the layer hidden in the inside of the membrane. The phospholipid bilayer is the most permeable to small, uncharged solutes. Protein channels float through the phospholipids, and, collectively, this model is known as the fluid mosaic model. E.g. Cellulose esters like cellulose acetate, cellulose acetate butyrate, cellulose triacetate and ethyl cellulose and Eudragits⁹.

Wicking agents

A wicking agent is a type of material with the ability to draw water in to the porous network of a delivery device

E.g. colloidal silicon dioxide, kaolin, titanium dioxide, SLS, low molecular weight (PVP).

Pore forming agents

These agents are particularly used in the pumps developed for poorly water soluble drugs and in the development of controlled porosity osmotic pumps. These pore forming agents cause the formation of micro porous membrane. Alkaline metal salts such as sodium chloride, sodium bromide, potassium chloride, potassium sulfate, potassium phosphate, etc.

Plasticizers

Different types and amount of plasticizers used in coating membrane also have a significant importance in the formulation of osmotic systems. They can change visco-elastic behavior of polymers and these changes may affect the permeability of the polymeric films. Some of the plasticizers used are as below

Polyethylene glycols

1. Ethylene glycol monoacetate; and diacetate- for low permeability
2. Tri ethyl citrate
3. Diethyl tartarate or Diacetin- for more permeable films

Classification of ODDS

1. Implantable osmotic pump.
2. Oral osmotic pump.

Implantable osmotic pump

They are either for experimental (animal) or for human use,

ALZET

ALZET osmotic pumps are miniature, implantable pumps used for research in mice, rats, and other laboratory animals. These infusion pumps continuously deliver drugs, hormones, and other test agents at controlled rates from one day to six weeks without the need for external connections or frequent handling. Their unattended operation eliminates the need for repeated nighttime or weekend dosing¹⁰. Alzet osmotic pumps Empty reservoir within the core of the pump is filled with the drug or hormone solution to be delivered and is surrounded by salt chamber with impermeable layer between them.

Mechanism – ALZET pumps operate because of an osmotic pressure difference. The rate of delivery by an Alzet pump is controlled by the water permeability of the pump's outer membrane. Thus, the delivery profile of the pump is independent of the drug formulation dispensed. Drugs of various molecular configurations, including ionized drugs and macromolecules, can be dispensed continuously in a variety of compatible vehicles at controlled rates. The molecular weight of a compound, or its physical and chemical properties, has no bearing on its rate of delivery by ALZET pumps. Water enters into the salt chamber through semipermeable membrane and causes compression of flexible reservoir and delivery of drug solution.

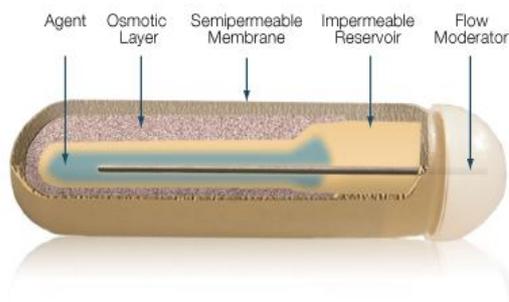


Fig. 4: Alzet osmotic pump

Applications

The alzet pump the enabled to Neuroscientist to manipulate the central & peripheral nervous system of an unstrained animal permitting simultaneous study of behavioral of motor & sensory function also neuro generative disease , drug dependence & tolerance & regulation.

Alzet pump have proved useful in biotechnology. For characterizing novel protein & peptide's such as growth factor, while also facilitating exciting new research in which antisense oligonucleotides.

For human use

Duros

It is a miniature, implantable osmotic pumps for long term, parenteral, delivery of drug in human. The system consists of an outer cylindrical titanium alloy reservoir. This reservoir has high-impact strength and protects the drug molecules from enzymes, body moisture, and cellular components that might deactivate the drug prior to delivery. At one end of the reservoir is positioned the membrane, constructed from a specially designed polyurethane polymer. The membrane is permeable to water but substantially impermeable to ions. Positioned next to the membrane is the osmotic engine. Next to the engine is the piston. The piston is made from elastomeric materials and serves to separate the osmotic engine from the drug formulation in the drug reservoir compartment. At the distal end of the titanium cylinder is the exit port. Exit ports can range from simple, straight channels to more complicated design configurations. The exit port design must be coupled to the rheological properties of the drug formulation. Duros implant with diameters up to 7mm have been designed , resulting in drug formulation volume of the 4mm*45mm implant has a total volume of less than 200microlit¹¹.

Mechanism -Through osmosis, water from the body is slowly drawn through the semi-permeable membrane into the pump by osmotic agent residing in the engine compartment, which expands the osmotic agent and displaces a piston to dispense small amounts of drug formulation from the drug reservoir through the orifice.

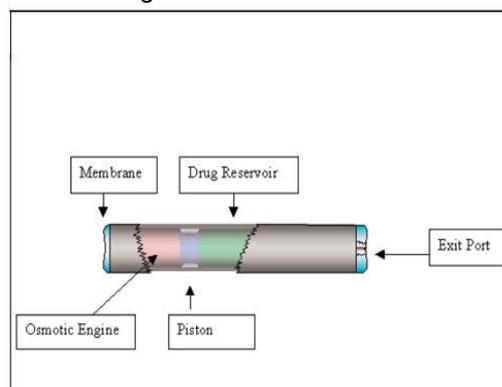


Fig. 5: Duros osmotic pump

Compounds delivered using DUROS® Technology

DUROS® has the potential to provide more flexibility than competitive products regarding the types of drugs that can be administered, including proteins, peptides and genes because the drug dispensing mechanism is independent from the drug substance¹¹.

Applications

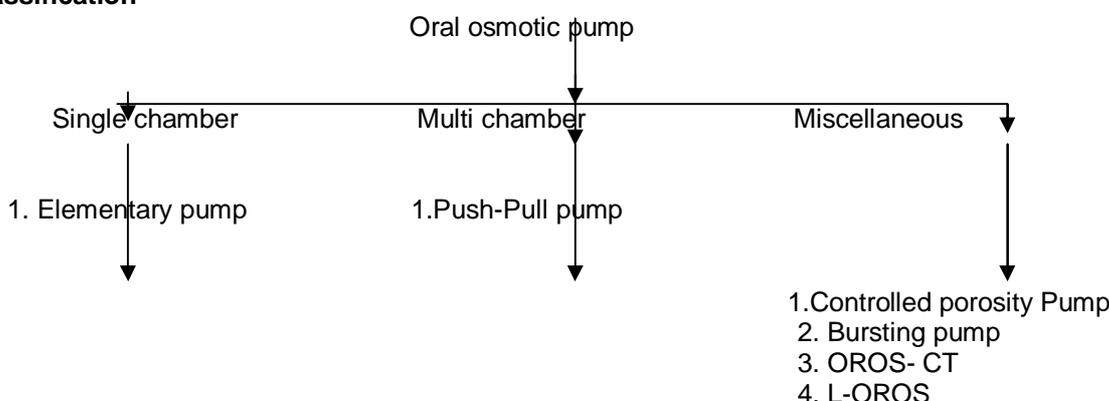
1) Duros Leuprolide Implant-the duros leuprolide implant has been designed to provide an alternative to periodic depot

injection leuprolide for palliative treatment of advanced prostate cancer.

2) Salmon calcitonin (sCT) has been used for the treatment of osteoporosis and Paget's disease where calcitonin inhibits osteoclastic bone resorption and induces calcium uptake.

3) Systemic or site-specific administration of a drug. The preferred site of implantation is subcutaneous placement in the inside of the upper arm. When implanted, a large, constant **osmotic** gradient is established between the tissue water and the osmotic engine.

Oral osmotic pump Classification



Single chamber osmotic system Elementary Osmotic Pump (EOP)

The elementary osmotic pump is a new delivery system for drugs. It delivers the agent by an osmotic process at a controlled rate. Control resides in the: a) Water permeation characteristics of a semi permeable membrane surrounding the formulating agent b) Osmotic properties of the formulation¹².

In its simplest embodiment the system is constructed by coating an osmotically active agent with the rate controlling 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. This osmotic imbibitions of water result in formation of a saturated solution of drug with in the core, which is dispensed at controlled rate from the delivery orifice in the membrane. Though 60 -80 percent of drug is released at a constant rate from the EOP, a lag time of 30-60 minute is observed in most of the cases as the system hydrates before zero order delivery from the system begins.

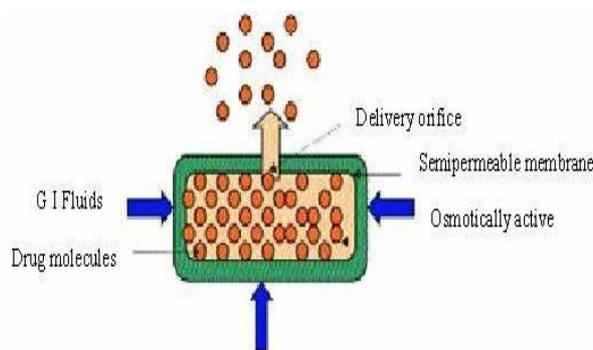


Fig. 6: Elementary Osmotic Pump (EOP)
Core- API ± osmogents Coat- Semi permeable membrane with delivery orifice

Multi-chamber osmotic systems Push-pull osmotic pump

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 (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 situ¹³. When this tablet later imbibes water, the other layer contains osmotic and coloring 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 semipermeable 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.

Core Tablet: Layer 1: API ± osmogents Layer 2: Polymeric osmotic agents
Coat: Semi permeable membrane with delivery orifice.

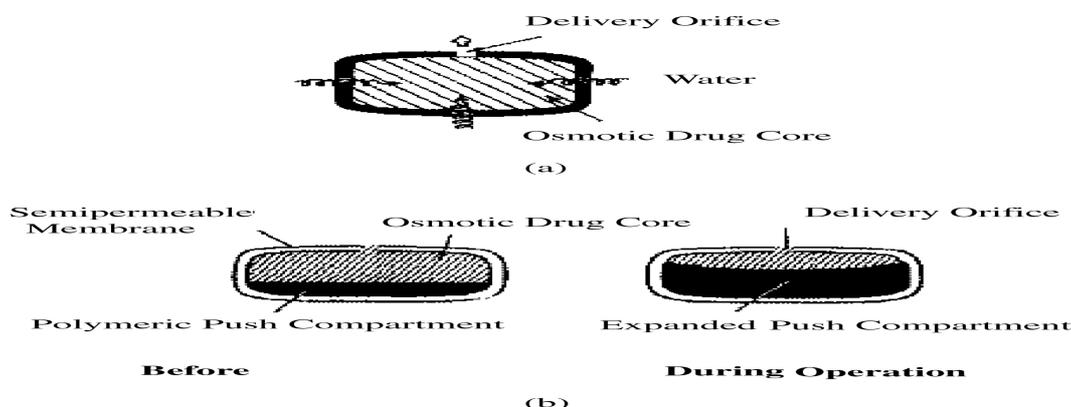


Fig. 7: Schematic diagram of an elementary osmotic pump (a) and a push-pull osmotic pump (b)

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 agent's 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 mucosa¹³.

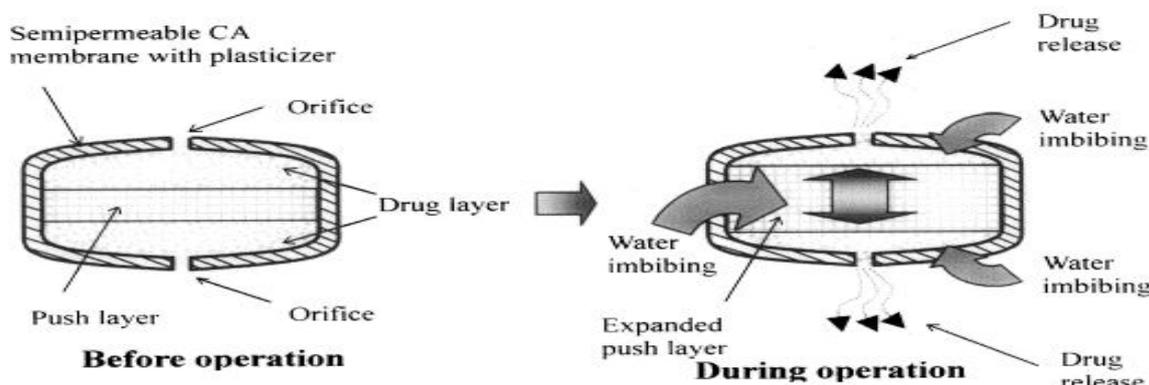


Fig. 8: sandwiched osmotic pump

Core tablet 3 layers Middle layer: push layer, 2 attached layers: API, Coat Semi permeable membrane with two side delivery orifice.

Miscellaneous oral osmotic pump

Controlled-porosity osmotic pump (CPOP)

The pump can be made with single or multicompartment dosage form, in either form,

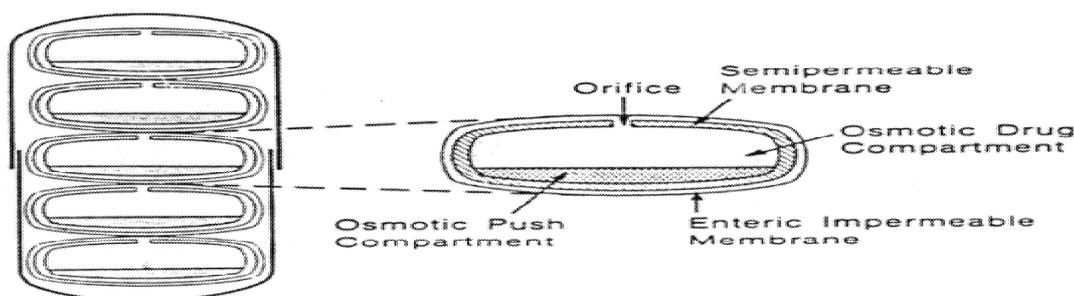


Fig. 11: OROS-CT

Liquid OROS L-OROS

Liquid OROS controlled release systems are designed to deliver drugs as liquid formulations. Liquid API formulation is present in a soft gelatin capsule, which is surrounded with the barrier layer, the osmotic layer, and the release rate-controlling membrane. A delivery orifice is formed through these three layers.

L-OROS Soft cap

The liquid drug formulation is present in a soft gelatin capsule, which is surrounded with the barrier layer, the osmotic layer, and semi permeable membrane. A delivery orifice is formed through these three layers. When the system is in contact with the aqueous environment, water is imbibed & results in the development of hydrostatic pressure inside the system forcing the liquid formulation to break through the hydrated gelatin capsule shell at the delivery orifice²¹.



Fig. 12: Schematic diagram of L-OROS Soft cap

Ruminal osmotic bolus pump

The RUTS push-melt osmotic system consists of an injection-molded semi permeable membrane that encapsulates an osmotic tablet, a partition layer, drug formulation and an iron densifier. System can vary in size from 2 to 3 cm in diameter and up to 10 cm in length, with overall drug loading capacity of up to 10gm.in the aqueous environment of the rumen, water is imbibed through the semi permeable membrane into the osmotic tablet, which swells and pushes against the partition layer. The semi permeable membrane controls the rate of water imbibition and therefore the pumping rate of the system this membrane composed of cellulosic esters and plasticizers, must be rigid enough to ensure device integrity the osmotic tablet consists of a swelling hydrogel (e.g. sodium carbomax), which provide a high osmotic gradient (more than 300atm) across the membrane. Between the

osmotic tablet and drug formulation layer is the partition layer, which acts like a plunger in the syringe to ensure a smooth response to the swelling of the osmotic tablet. It contain compound with a higher melting point or a higher viscosity than the drug formulation layer²².

Site of administration – ruts push-melt technology was developed to meet the need for drug –dedicated osmotic system for use in ruminant production animal. Ruminant such as cattle and sheep have a complex digestive system that includes a large four –chambered stomach; the chamber are the rumen, the reticulum, the omasum and the abomasum. In the rumen, ingested cellulose is broken down by microorganism into simple mono-and disaccharides suitable for digestion. Orally administered sustained – release delivery system are typically limited by the target animal git transit time, but in ruminants (cattle,

goats and sheep) the transmit time can be controlled by using a device with sufficient density or a geometrical configuration that

keeps it in the rumen if for an indefinite period²².

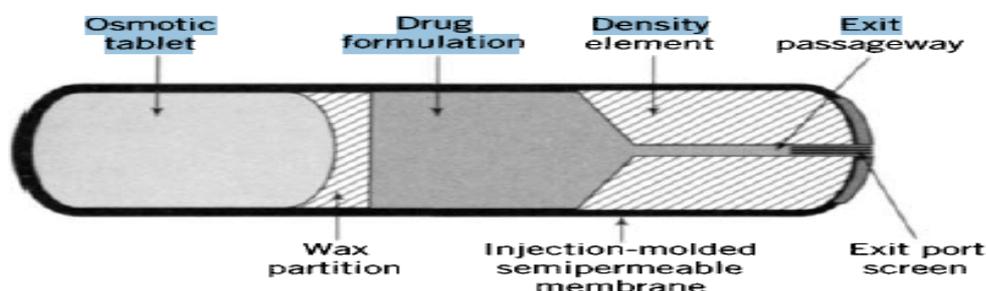


Fig. 13: Cross section of the Push-Melt® Ruminal Therapeutic System (RUTS)

RUTS Push-melt system can be designed for a variety of drug delivery profiles such as zero order, pulsatile ascending, or descending. They are typically designed for zero-order drug delivery of up to 5gm/day for duration ranging from 1day to 1year.

Application

The RUTS Push-melt osmotic system is an innovative adaptation of osmotic technology for the delivery of agents to ruminants. It is developed for the delivery of a potent parasiticide, and sodium selenite, a nutritional supplement antibiotics, growth promoter and estrus suppressants.

Formulation factors affecting drug release rate of ODDS's

Orifice size

The size of the orifice must be larger than a minimum size (0.075mm), to minimize hydrostatic pressure. This is necessary step in achieving zero order drug release. The size of the orifice must be smaller than a maximum size (0.274 mm), to minimize diffusion contribution to delivery rate.

Laser drill

This technology is well established for producing sub-millimeter size hole in tablets. Normally, CO₂ laser beam (with output wavelength of 10.6μ) is used for drilling purpose, which offers excellent reliability characteristics at low costs.

Solubility

APIs for **osmotic** delivery should have water solubility in the desired range to get optimize drug release. However, 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. The

release rate depends on the solubility of the solute inside the drug delivery system. Therefore, drugs should have sufficient solubility to be delivered by osmotic delivery. Various solubility modifying approaches include:

1. Use of swellable polymers: vinyl acetate copolymer, polyethylene oxide have uniform swelling rate which causes drug release at constant rate²³.
2. Use of effervescent mixtures: Mixture of citric acid and sodium bicarbonate which creates pressures in the **osmotic** system and ultimately controls the release rate.^{7,8}
3. Use of cyclodextrin derivatives they are known to increase solubility of poorly soluble drugs. The same phenomenon can also be used for the **osmotic** systems²⁴.
4. Use of encapsulated excipients: Solubility modifier excipient used in form of mini-tablet coated with rate controlling membrane²⁵.
5. Resin Modulation approach: Ion-exchange resin methods are commonly used to modify the solubility of APIs. Some of the resins used in **osmotic** systems are Poly (4-vinyl pyridine), Pentaerythritol, citric and adipic acids²⁶.
6. Use of crystal habit modifiers: Different crystal form of the drug may have different solubility, so the excipient which may change crystal habit of the drug can be used to modulate solubility²⁷.
7. Co-compression of drug with excipients: Different excipients can be used to modulate the solubility of APIs with different mechanisms like saturation solubility, pH dependent solubility. Examples of such excipients are organic acids, buffering agent, etc²⁸.

Osmotic pressure

The next release-controlling factor that must be optimized is the **osmotic** pressure gradient between inside the compartment and the external environment. The simplest and most predictable way to achieve a constant **osmotic** pressure is to maintain a saturated solution of **osmotic** agent in the compartment. The following table shows osmotic pressure of commonly used solutes in CR formulations¹⁴.

Advantage

1. They typically give a zero order release profile after an initial lag.

2. Deliveries may be delayed or pulsed if desired.
3. Drug release is independent of gastric pH and hydrodynamic condition.
4. The release mechanisms are not dependent on drug.
5. A high degree of in-vitro and in vivo correlation
6. Higher release rates are possible with osmotic systems compared with conventional diffusion-controlled drug delivery systems.
7. The release from osmotic systems is minimally affected by the presence of food in gastrointestinal tract

Table 2: ODDS formulation available in market

| Drug | Osmotic agent | Polymer osmogents | Formulation | Dose |
|---------------------------|--------------------|--------------------------------|----------------------------|---------------------|
| Isradipine | Magnesium sulphate | Sodium carboxymethyl cellulose | Push -Pull | 5, 10 mg |
| Pseudoephedrine | Sodium chloride | Hydroxypropylmethyl cellulose | Elementary pump | 60 mg IR, 180 mg CR |
| Nifedipine | Sodium bicarbonate | Hydroxypropylmethyl cellulose | Sandwiched Osmotic tablet | 10, 20 mg |
| Chlorphen Iramine meleate | Sodium sulphate | Methylcellulose | Elementary pump | 4mg IR, 12mg CR |
| Glipizide | Potassium chloride | Polyethylene oxide | Push - Pull | 5, 10 mg |
| Verapamil | Potassium chloride | Polyvinyl pyrrolidone | Push -Pull with time delay | 180, 240 mg |
| Phenylpro Panolamine | Sodium chloride | Polyethylene oxide | Elementary pump | 75 mg |
| Prazosin | Potassium chloride | Hydroxypropylmethyl cellulose | Push -Pull | 2.5 - 5 mg |

CONCLUSION

In Osmotic Drug Delivery system (ODDS), osmotic pressure provides the driving force for drug release. Major advantage is controlled drug release by zero order. The ODDS mainly reside in their capacity to deliver a drug at predetermined rate, independent of physiological parameter such as food intake, patient age, and pH of G. I. tract. Most of the ODDS device is designed by modifying the Rose-Nelson pump and Higuchi-Theeuwes pump. There are many marketed product long term therapy for diabetes, hypertension, other chronic disease of ODDS. Other than Oral ODDS implant that work on osmotic principle are promising for wide variety of molecule for long period of time. In the biotechnology industry there are many newer and potent drug are discovered they need to deliver such a constant in constant rate, the ODDS play important role in future. Now a day's large variety of ODDS technology available allows an interesting adaptation of the system to the drug property and the dosage strength.

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