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Osmotic Pump Drug Delivery Devices: From Implant to Sandwiched Oral Therapeutic System

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Abstract: Osmotic systems utilize the principle of osmotic pressure for the delivery of drugs. Drug release from these systems is independent of pH and other physiological parameter to a large extent and it is possible to modulate the release characteristic by optimizing the properties of drug and system[3, 4]. Pressure generated by the osmotic flow of water through a semi permeable membrane in to an aqueous compartment containing solute at higher concentration[5]. A number of design options are available to control or modulate the drug release from a dosage form. Majority of per oral dosage form fall in the category of matrix, reservoir or osmotic system. In matrix system, the drug is embedded in polymer matrix and the release takes place by partitioning of drug into the polymer matrix and the release medium.
Keywords: polymer matrix, drug release, osmotic system, reservoir

Introduction

The first report of an osmotic effect dates to Abbenollet {1748}. But Pfeffer obtained the first quantitative measurement in 1877. The novel system of drug delivery offer a means of improving the therapeutic effectiveness of incorporated drug by providing sustained, controlled delivery and or targeting the drug to desired site[1]. Movement of solvent (water) through a semi permeable (permeable only to the solvent) membrane from in area of low solute concentration to an area of high solute concentration[2].

Osmotic Drug Delivery Devices[7, 8]

They fall in two categories,

Implantable: a) The Rose and Nelson Pump **b)** Alzet osmotic pump **c)** Higuchi Leeper Pump **d)** Higuchi Theuwes pump

Oral osmotic Pump: a) Single chamber osmotic pump **b)** Elementary osmotic pump

Multi chamber osmotic pump a) Push pull osmotic pump **b)** Osmotic pump with non expanding second chamber

Specific types of osmotic pumps a) Controlled porosity osmotic pump **b)** Osmotic bursting osmotic pump **c)** Liquid OROS **d)** Delayed Delivery Osmotic device **e)** Telescopic capsule **f)** Oros ct (colon targeting) **g)** Sandwiched oral therapeutic system **h)** Osmotic pump for insoluble drugs **i)** Monolithic osmotic systems

Implantable osmotic pump This is most versions in the category of implantable pumps developed by Alza Corporation as shown in fig it is composed of three concentric layers-the drug reservoir, the osmotic sleeves and the rate controlling semi permeable membrane. The additional component called flow moderator is inserted into the body of the osmotic.

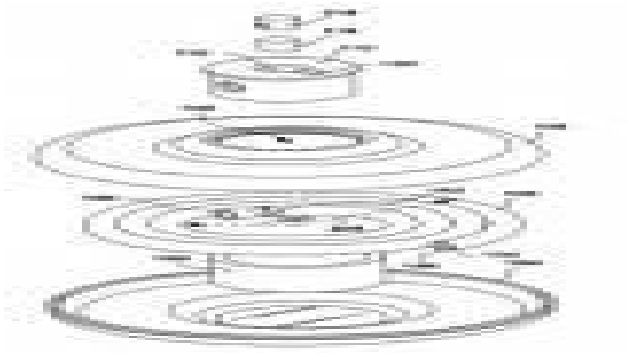

Figure: Implantable osmotic pump[21].

The inner most compartment of drug reservoir which is surrounded by an osmotic sleeve, a cylinder containing high concentration of osmotic agent. The osmotic sleeve is covered by a semi permeable membrane when the system is placed in aqueous environment water enters the sleeve through semi permeable membrane, compresses the flexible drug reservoir and displaces the drug solution through the flow moderator. These pumps are available with variety of delivery rates between 0.25 to 10ml per hour and delivery duration between one day and four weeks.

The Rose Nelson Pump[1] In, 1955, two Australian physiologists reported the first osmotic pump. They were interested in delivery of drug to the gut of sheep and cattle. The pump consisted of three chambers (fig.5) a drug chamber with an orifice, a salt chamber with elastic diaphragm containing excess solid salt, and a water chamber. A semipermiable membrane separates the drug and water chamber. The difference in osmotic pressure across the membrane moves water from the water chamber in to the salt chamber. The volume of 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.

Alzet osmotic pump[9, 12] ALZET pumps operate because of an osmotic pressure difference between a compartment within the pump, called the salt sleeve, and the tissue environment in which the pump is implanted. The high osmolality of the salt sleeve causes water to flux into the pump through a semi permeable membrane which forms the outer surface of the pump. As the water enters the salt sleeve, it compresses the flexible reservoir, displacing the test solution from the pump at a controlled, predetermined rate. Because the compressed reservoir cannot be refilled, the pumps are designed for single-use only.

Figure: Alzet osmotic pump

Higuchi osmotic pump[1] Design of Higuchi leeper pump described in fig. represents the first simplified version of alzet pump. It contains rigid housing and the semi permeable membrane, which is supported on a perforated frame. Rigid housing divides in two chambers by a movable separator. The benefit over rose nelson pump is that it does not have 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 and months prior to use.

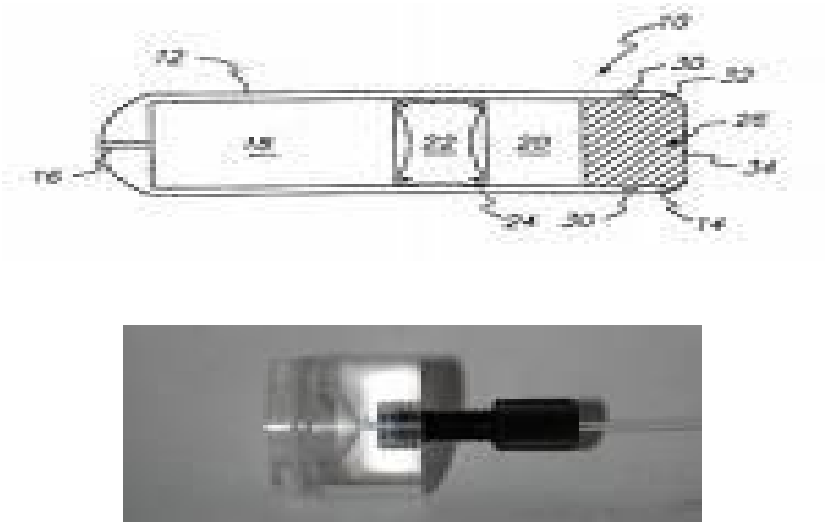

Figure: Higuchi osmotic pump

Oral osmotic pump

Elementary Osmotic Pump[10, 11] 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 formulation

In its simplest embodiment the system is constructed by coating an osmotically active agent with the rate controlling semi permeable 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. These system are suitable or delivery of drugs having moderate water solubility.

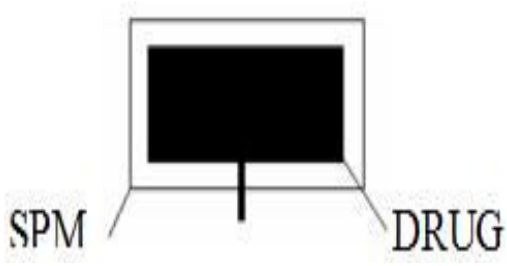

Figure: Elementory osmotic pump

Multi chamber osmotic pump

Push Pull Osmotic Pump[12, 13] 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 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 Pump With Non Expanding Second Chamber[14] The second category of multi-chamber devices comprises system containing a non-expanding second chamber. This group can be divided into two sub groups, depending on the function of second chamber. In one category of these devices, the second chamber is used to dilute the drug solution leaving the devices. This is useful because in some cases if the drug leaves the oral osmotic devices a saturated solution, irritation of GI tract is a risk.

Specific types of osmotic pump: Osmotic Brusting Osmotic Pump[15] this system is similar to an EOP expect 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 semi permeable membrane can control release of drug. This system is useful to provide pulsated release

Liquid Oral Osmotic System[16, 17]Liquid OROS are designed to deliver drugs as liquid formulations and combine the benefits of extended release with high bioavailability. They are of two types: a) L OROS hard cap b) L OROS soft cap

Delayed liquid bolus delivery system Each of these systems includes 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, there by forcing the liquid formulation to be delivered from the delivery orifice. Where as L OROS hard cap or soft cap system is designed to provide continuous drug delivery, the L OROS 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 I to 10 hour, depending on the permeability of the rate controlling membrane and thickness of the placebo layer.

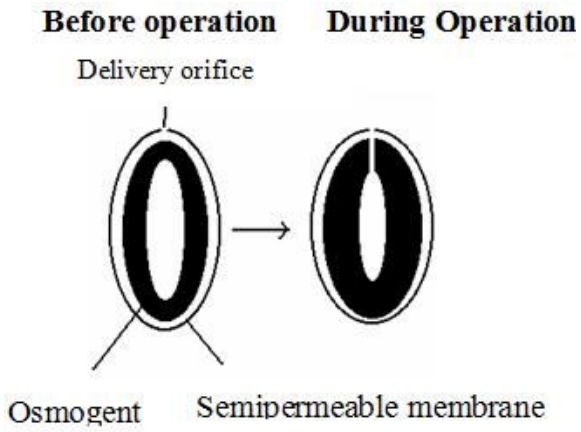

Figure: delayed liquid bolus delivery system

Delayed Delivery Osmotic Device[18, 19] Because of their semi permeable walls, an osmotic device inherently show lag time before drug delivery begins. Although this characteristic is usually cited as a disadvantage, it can be used advantageously. The delayed release of certain drug (drugs for early morning asthma or arthritis) may be beneficial. The following text describe other means to further delay drug release

Telescopic Capsule for Delayed Release 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 sections. 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 slid able 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

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

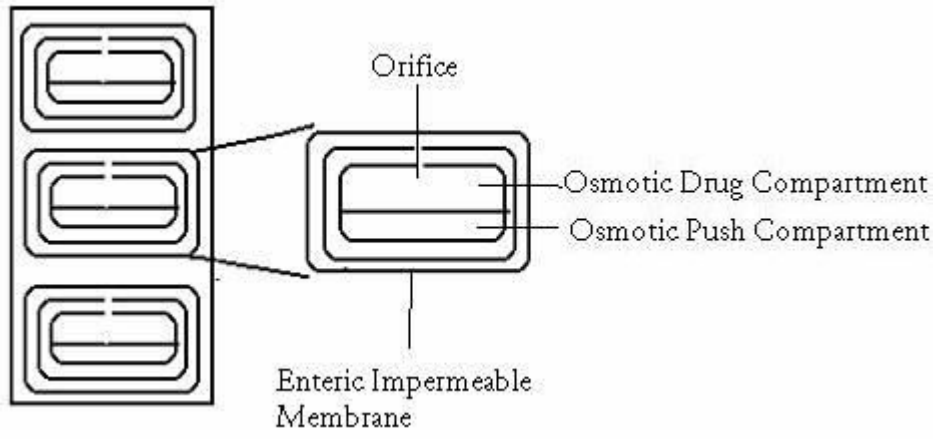

Figure: Illustration of OROS-CT

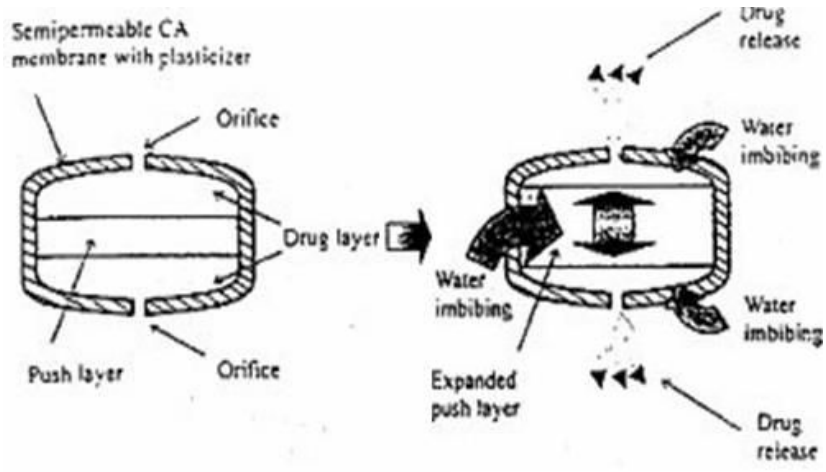

Figure: Sandwiched osmotic tablets

After coming in contact with the gastric fluids, gelatin capsule dissolved and the enteric coating prevents entry of fluids from stomach to the system as the system enters into the small intestine the enteric coating dissolves and water is imbibed into the core thereby causing the push compartment to swell. At the same time flow able gel is formed in the drug compartment, which is pushed out of the orifice at a rate, which is precisely controlled, by the rate of water transport across the semi permeable membrane.

Sandwiched Osmotic Tablets (SOTS) [20] 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 mucosa.

Monolithic Osmotic System[21] It constitutes a simple dispersion of water-soluble agent in polymer matrix. When the system comes in contact in with the aqueous environment. Water imbibtion 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.

Osmat[22] It is a novel osmotically driven matrix system, which utilizes the hydrophilic polymers to swell, and gel in aqueous medium forming a semipermiable 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.

Controlled Porosity Osmotic Pump[23, 24] 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. 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 allued to above. The rate of flow dv/dt of water into the device can be represented as

$$dv / dt = Ak / h (Dp-DR)$$

Where k = Membrane permeability
A = Area of the membrane
Dp = Osmotic pressure difference
DR = Hydrostatic pressure difference

Characteristics of osmotic pumps[1]

Research Use	Route of Administration	Duration of Steady-state Delivery(hr)	Filled Volume (Ml)	Steady-State Delivery Rate (Lµl/ Hr)	Distinguishing Terminology
Clinical Research	Oral	12	0.2	15.0	Oral pump
Clinical Research	Oral	24	0.2	8.0	Oral pump
Clinical Research	Rectal/ vaginal	30	2.0	60	Rectal pump
Animal Research	Implant	168	0.2	1.0	Mini-osmotic pump
Animal Research	Implant	336	0.2	0.5	Mini-osmotic pump
Animal Research	Implant	168	2.0	10	osmotic pump
Animal Research	Implant	336	2.0	5.0	osmotic pump

Conclusion

In recent years, novel drug delivery system (NDDS) has been recognized as an attractive niche for the pharmaceutical and health industry. Among various NDDS, osmotic pumps have matured from their use with laboratory animals to the most reliable controlled release systems for humans. Osmotically controlled drug delivery system use 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. Because of their unique advantages over other types of dosage forms, osmotic pumps from a class of their own among the various drug delivery technologies, and a variety of products based on this technology are available on the market. This article is a review of different types of osmotic pumps and their role in drug delivery.

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