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Review Article

A REVIEW ON OSMOTICALLY CONTROLLED DRUG DELIVERY SYSTEMS

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ABSTRACT:-

Osmotically controlling drug delivery system is one of the best method of drug technology it is highly fruitful and effective. In this osmotic pressure is used to deliver drug properly as osmosis is the movement from lower concentration to the higher concentration. By this system we can release drug in proper manner as it is widely accepted technique with interesting facts and use. There are various drug delivery components like drugs. Osmotic agent and semi permeable membrane all are essential and have their own role to play, It is one of the best in best method used now a days to get best results.

Key words: Osmotic, Osmosis Delivery, Pump, Solvent, ALZET, Telescopic, Surfactant, Polymer.

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INTRODUCTION:-

OCDDS stands for osmotically controlled drug delivery systems. OCDDS is one of the most common and promising drug delivery system that is done by using osmotic pressure as a driving force for the control delivery of active agent. The drugs which deliver through this system are not dependent on hydrodynamic and pH conditions of the body. It is also possible to obtain higher release rates through these systems than through other diffusion-based systems. To fulfill patient's need and requirement various type of osmotic pumps for different drugs are available in market. Recently research in field of pharmaceutical shows development of several novel drug delivery systems. The main motive of newly develop drug product is to be therapeutically effective with some additional benefits such as:

- Reduced side effects
- Bioavailability of drug could be increased

- In chronic condition effectiveness could be grater
- Dose frequency could be decreased
- Delivery profile of the drug can be modified
- simplified dosing schedule can improve patient medication use
- consistent blood plasma level within the therapeutic window¹

Osmosis:-

Movement of solvent molecules from lowers concentration to higher concentration across the semi permeable membrane; the phenomenon is known as osmosis. When the excess of solvent molecules passing in one direction creates a pressure called 'osmotic pressure'. The release rate of drug by osmotic drug delivery system is depends upon solubility, molecular weight, activity coefficient of the solute (osmogen) and osmogen. The osmogen is coated with a semipermeable

membrane which has one or more delivery ports through which the drug is released over time.

Principles of Osmosis:-

The first report of an osmotic effect dates to Abbenollet. but first quantitative measurement was obtained by Pfeffer in 1877. In his analysis he separates a sugar solution from pure water by a membrane permeable to water but impermeable to sugar². A flow of water then takes place into the sugar solution that cannot be halted until a pressure π is applied to the sugar solution. Pfeffer showed that this pressure, the osmotic pressure π of the sugar solution is directly proportional to the solution concentration and the absolute temperature. Within few years, Vant Hoff had shown the analogy between these results and ideal gas laws by the expression:-

$$\pi = \phi c RT$$

Where, p = Osmotic pressure, π = osmotic coefficient, c = molar concentration, R = gas constant T = Absolute temperature. Where, p = Osmotic pressure, π = osmotic coefficient, c = molar concentration, R = gas constant T = Absolute temperature. Osmotic pressure is having colligative properties that are properties of solution which is depend upon the ratio of number of solute particle to the number of solvent molecule present in the solution and not on the nature of the chemical present in the solution. The solution which have different conc. but have same solute and solvent system exhibit their conc. directly proportional to osmotic pressure. Thus it is helpful to achieve a constant osmotic pressure and constant influx of water which result in constant zero order release rate of drug. In controlled release formulation osmotic pressure is ranging from 30 atm (sodium phosphate) and upto 500 atm (lactose, fructose mixture). Equation showing osmotic water flow through a membrane is given bellow:-

$$dv/dt = A Q \Delta \pi / L$$

Where dv/dt = water flow across the membrane of area A in cm^2 , L = thickness, Q = permeability and $\Delta \pi$ = the osmotic pressure difference between the two solutions on either side of the membrane. This equation showing that osmotic agent is not permeable through the membrane but the membrane is permeable to water³.

Osmotically Controlled Drug Delivery Systems⁴:-

In the osmotic Controlled drug delivery system to release the drug in controlled manner the osmotic pressure is used as driving force. For the same purpose different techniques are used but this technique is most interesting and widely acceptable. Detailed research has been done on the osmotic system and some of the patients are also published. In this Drug can administer by both oral and parenteral route. Gastro-intestinal therapeutic systems (GITS) are also known as oral osmotic system while implantable pumps are used for parenteral osmotic drug delivery.

Basic components of osmotically controlled drug delivery system (Osmotic Pumps):-

- Drug
- Osmotic agent
- Semi permeable membrane
- Plasticizers
- Hydrophilic and hydrophobic polymer
- Wicking agent
- Surfactant
- Coating solvent

Drugs:-

Ideal Characteristics of drug for OCDDS

- Short biological half-life (2-6h)
- Highly potent drug
- Required for prolonged treatment e.g. Nifedipine, Glipizide, Virapamil.

Osmotic agents:-

Osmogents are organic as well as inorganic in nature, there are widely used for invention of osmotic dispensing device.

Inorganic water-soluble osmogents⁵:-

- Mag. Sulphate
- Sodium chloride
- Sod.sulphate
- Pot.chloride
- Sod.bicarbonate.

Organic polymer osmogents:-

- Sodium carboxymethyl cellulose
- Hydroxypropylmethylcellulose
- Hydroxyethylmethylcellulose,
- Methylcellulose
- Polyethylene oxide
- polyvinyl pyrrolidone.

Semi Permeable Membrane:-

For outer as well as inner environment of the device the nature of semi permeable membrane should be a stable. the membrane must be biocompatible it should be impermeable to the dispenser content so that osmogent can cross the membrane. The membrane must be firm to retain dimensional integrity of device.⁶

General criteria for Ideal Semi Permeable Membrane:-

The ideal Semi Permeable Membrane must have following properties:

- The material should have enough wet strength (-105) to retain its dimensional integrity throughout the operational lifetime of the device.
- To estimate water flux rate water vapor transmission rate is used so that to retain the water flux rate in the desired range, membrane exhibit sufficient water permeability.
- The membrane should also be biocompatible

Plasticizers:-

In the formulation of osmotic systems to coat the membrane, different type of plasticizer are used. It can change polymer visco-elastic behavior that may affect the polymeric films permeability. Some of the plasticizers used are as below:

- Polyethylene glycols
- Ethylene glycol monoacetate; and diacetate -for low permeability
- Tri ethyl citrate
- Diethyl tartarate or Diacetin- for more permeable films

Hydrophilic and hydrophobic polymer⁷:-

For making drug containing matrix core the polymers are used in the formulation development of osmotic systems. When highly water soluble compound co- entrapped in matrices which are hydrophobic in nature such compounds are obtained for controlled release water soluble compounds while compounds which are partially water soluble. In the development of osmotic pumps of water-soluble drugs mixture of hydrophilic and hydrophobic polymer can be used. Since due to their swelling nature they increase the hydrostatic pressure inside the pump, so in this case non-swelling polymers are used. Hydrophilic polymers such as hydroxy ethyl cellulose, carboxy methylcellulose, hydroxy propyl methylcellulose, high-molecular-weight poly(vinyl pyrrolidone), and hydrophobic polymers such as ethyl cellulose and wax materials can be used for this purpose.

Wicking agent:-

It is defined as the ability of the material to draw water into the porous network of a delivery device. Example of wicking agent is silicon dioxide, kaolin, titanium dioxide etc. The wicking agent allows the drug to increase its contact surface area with the incoming aqueous fluid. It is useful to enhance the rate of drug release from the cleft of the drug. It can be swellable or non-swelling in nature. They are characterized by having the ability to undergo physisorption with water. Physisorption is also known as physical absorption. In this atom's electronic structure is barely perturbed upon adsorption. In this function of wicking agent travel the water from surface to inside the core of tablet; this function is helpful to create channel/

network of increased surface area. Example- polyvinylpyrrolidone.

Surfactant⁸:-

Surfactants are particularly useful when added to wall-forming material. They produce an integral composite that is useful for making the wall of the device operative. Surfactants are particularly useful when added to wall-forming material. They produce an integral composite that is useful for making the wall of the device operative. Surfactants are amphiphilic in nature (which contain both hydrophobic and hydrophilic group) i.e., it contains both group water soluble and water insoluble. It play an important role in various formulation used in pharmaceutical aid. (detergents, emulsion, laxative etc.) Example of surfactants are- carboxylic acid salts, phosphoric acid esters.

Coating solvent⁹:-

Solvents which are suitable for making solution which are polymeric in nature that is used for manufacturing the wall of the osmotic device. The typical solvents include methylene chloride, acetone, methanol, ethanol, isopropyl alcohol, butyl alcohol, ethyl acetate, cyclohexane, carbon tetrachloride, and water. The mixtures of solvents such as acetone-methanol (80:20), acetone-ethanol (80:20), acetone-water (90:10), methylene chloride-methanol (79:21), methylene chloride-methanol water (75:22:3) can be used.

Advantages and disadvantages of Osmotically controlled drug delivery systems¹⁰:-

Advantages:-

The following are the advantages of osmotically controlled drug delivery systems:

- After an initial lag it can give a zero order release profile.
- Deliveries may be delayed or pulsed if desired.
- The release mechanisms are not dependent on drug.
- The release of drug is not depending upon the hydrodynamic condition and pH of GIT.

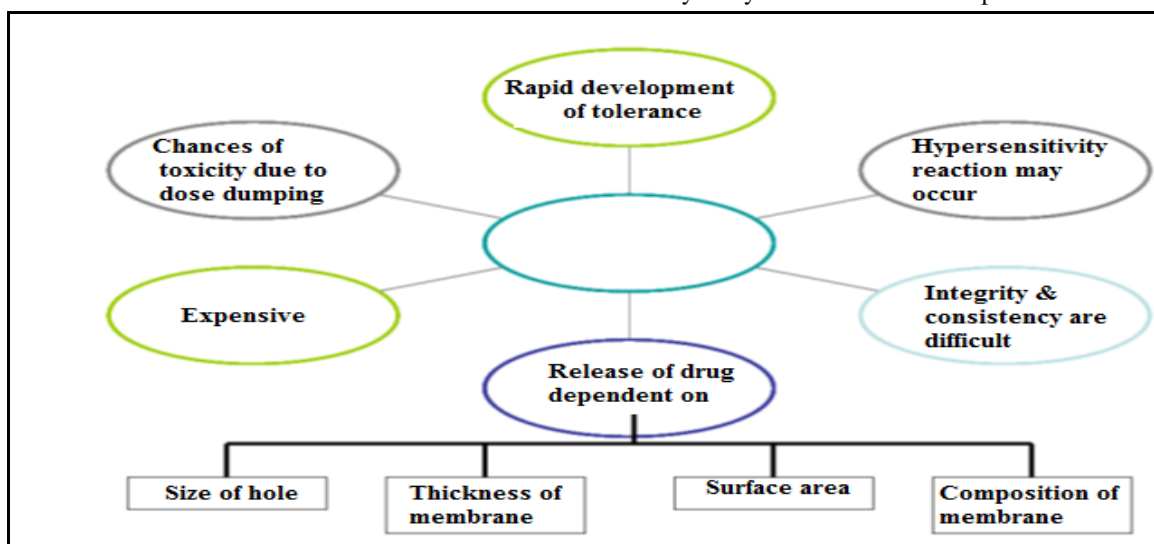


Fig:-1. Disadvantages of osmotic DDS

Disadvantages:-

- If the coating process is not well controlled there is a risk of film defects, which results in dose dumping
- Size hole is critical
- Dose dumping
- Retrieval therapy is not possible in the case of unexpected adverse events.
- Rapid development of tolerance.

General mechanism for drug release from osmotic pumps¹¹:-

As described earlier, the basic equation which applies to osmotic systems is:-

$$dM/dt = dV/dt \times c \dots\dots\dots(\text{eq 1})$$

Where, dM/dt = mass release, dV/dt = volumetric pumping rate, c = concentration of drug.

But, $dV/dt = (A/h) L_p (\sigma \Delta\pi - \Delta p)$

Where, A = membrane area, h = thickness of membrane, L_p = mechanical permeability, σ = reflection coefficient, $\Delta\pi$ = osmotic pressure difference, Δp = hydrostatic pressure difference.

As the size of orifice delivery increases, Δp decrease, so $\Delta\pi \gg \Delta p$ and equation becomes

$$dV/dt = A/h L_p (\sigma \Delta\pi)$$

When the osmotic pressure of the formulation is large compared to the osmotic pressure of the environment, p can be substituted for D_p .

$$dV/dt = A/h L_p \sigma \pi = A/hk \pi$$

($k = L_p \sigma$ = membrane permeability)

Now, equation (1) can be given as

$$dM/dt = (A/h) k \pi c = (A/h) k \pi S$$

(S = solubility of drug, c taken as S)

Type of osmotic pump¹²:-

Rose and Nelson Pump:

Rose and Nelson, the Australian scientists, were initiators of osmotic drug delivery. In 1955, they developed an implantable pump for the delivery of drugs to the sheep and cattle gut. This pump is composed of: a water chamber, a salt chamber (separated by a semipermeable membrane) and a drug chamber. The salt chamber is used to hold solid salt. The water flows from the water chamber towards salt chamber is affected by osmotic pressure across the membrane. Volume of salt chamber increases due to water flow and finely the drug is pumped out of the device.

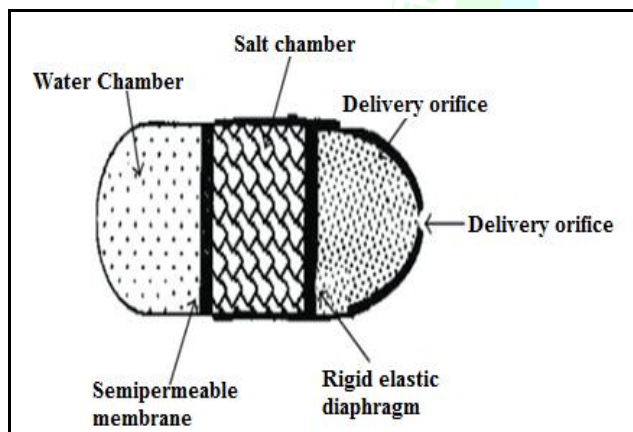


Fig:- 2. Rose and Nelson Pump

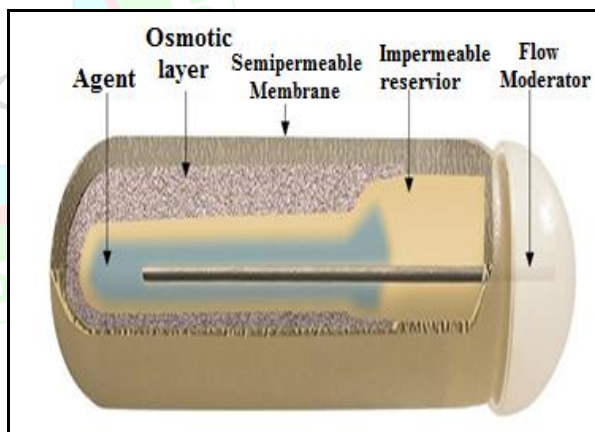


Fig:- 3. Alzet Osmotic Pump

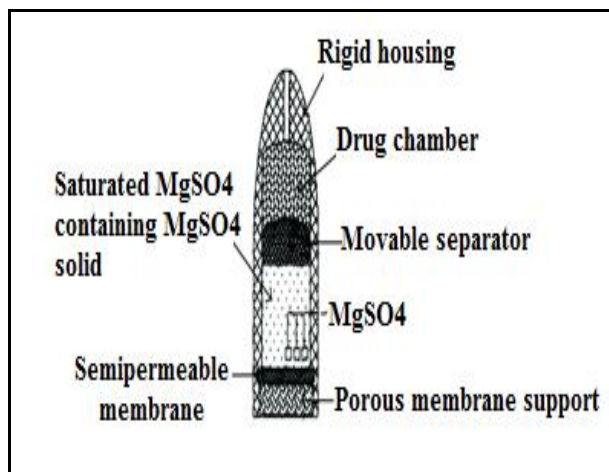


Fig:- 4. Higuchi Leeper Pump



Fig.5. Higuchi Osmotic Pump

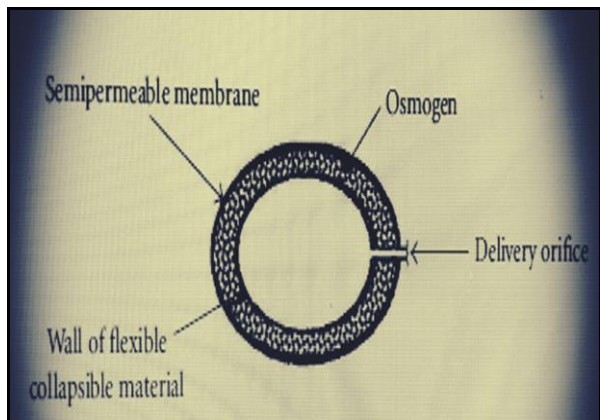


Fig:- 6. Higuchi Theeuwes Pump

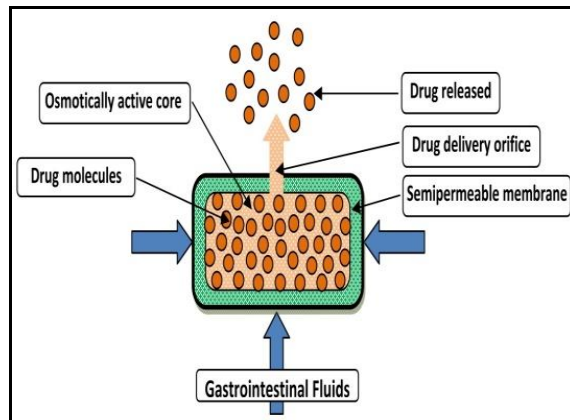


Fig:- 7. Elementary Osmotic Pumps

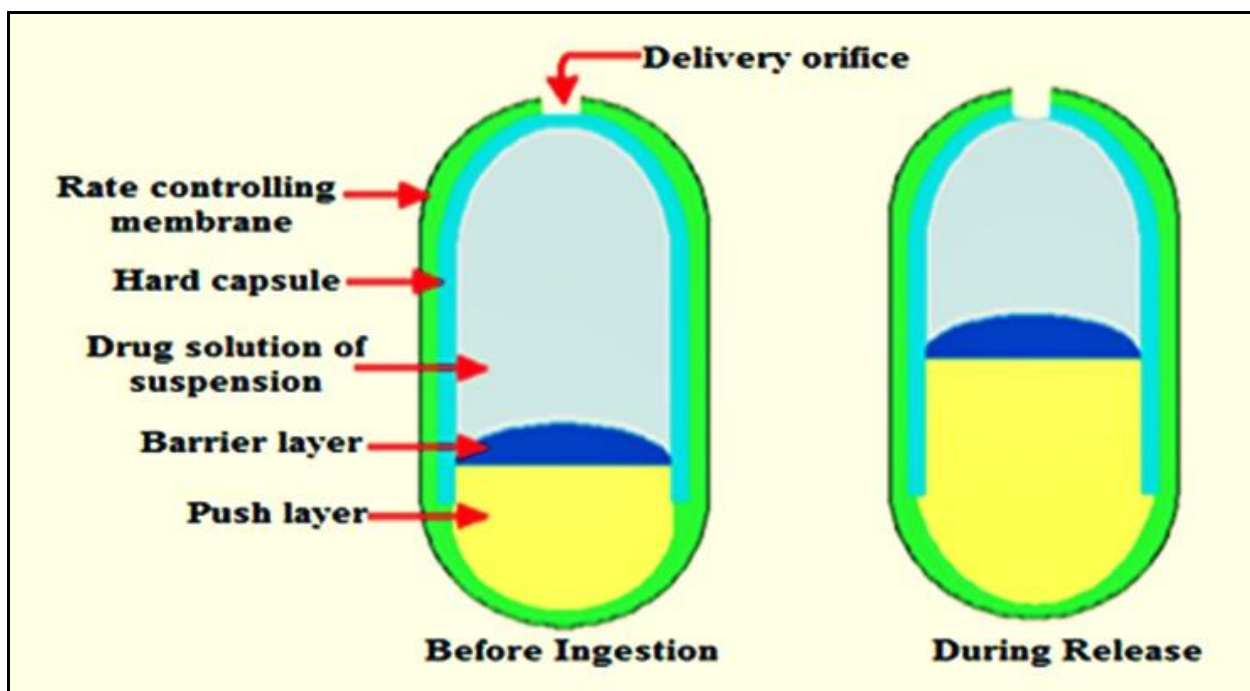


Fig:- 8. Push Pull Osmotic Systems

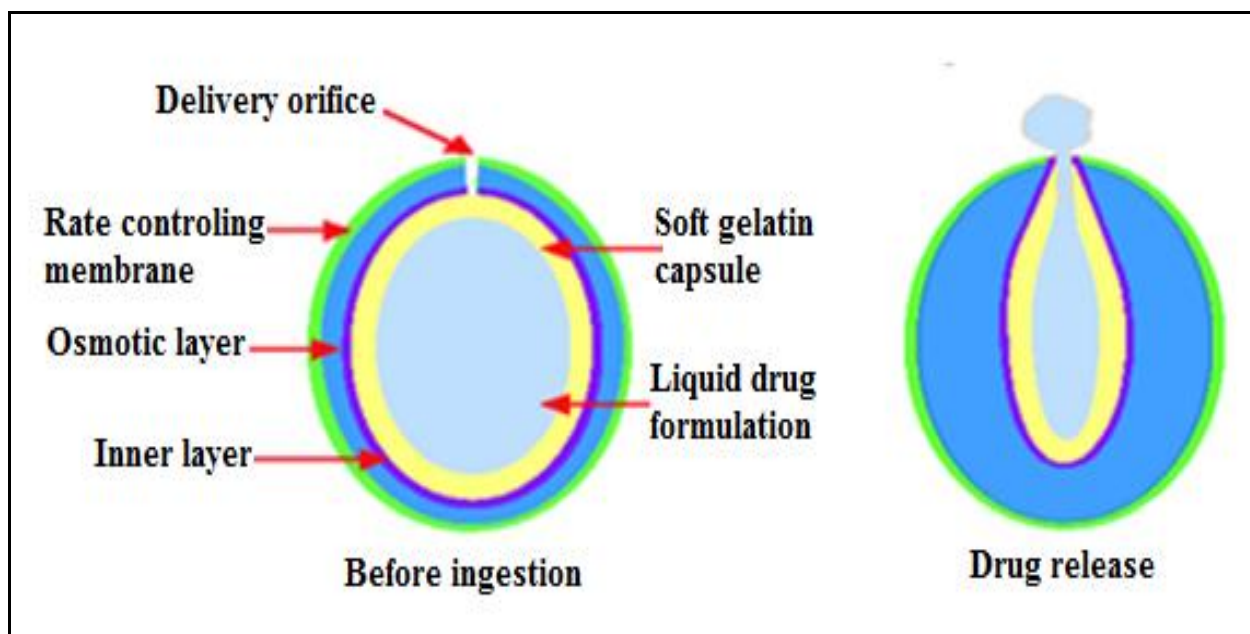


Fig:-9. OROS system before and during operation

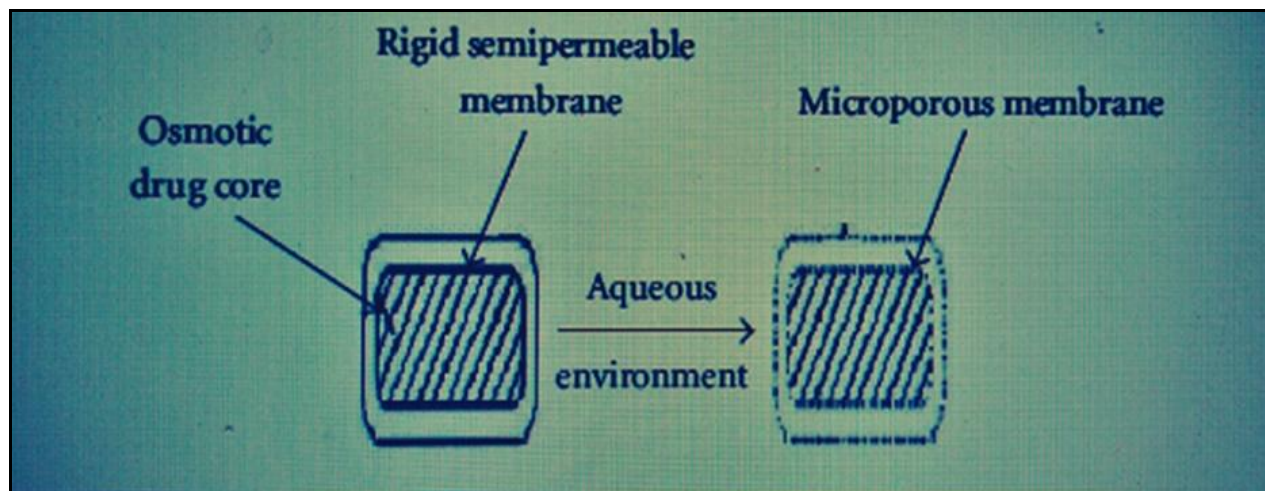


Fig:-10. Mechanism of action of controlled porosity osmotic pump

ALZET Osmotic Pump:-

It is 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 dosing. ALZET pumps operate by osmotic displacement. An empty reservoir within the core of the pump is filled with the drug or hormone solution to be delivered. ALZET pump can be given through intravenous, intracerebral, or intra-arterial infusion with the help of catheter. It can be used for targeted drug delivery to localize the drug effect. It is used to deliver the drug at particular organ or site; the liver, spinal cord, spleen, wound healing sites and organ or tissue transplants. ALZET pumps have been used successfully to deliver hundreds of different compounds, including antibodies, chemotherapeutic drugs, cytokines, growth factors, hormones, and peptides.

Higuchi-Leeper Osmotic Pump:-

Higuchi and Leeper have proposed a number of variations of the Rose-Nelson pump and these designs have been described in US patents. This pump has no water chamber and it is activated when there is diffusion of water from the surrounding environment. This variation allows the pump to be prepared loaded with drug and thus it can be stored for long period of time. This pump contains rigid housing and a semi permeable membrane supported by a perforated frame. When the biological fluid penetrate into the device with the help of porous and semipermeable membrane it get dissolve in $MgSO_4$ which create osmotic pressure inside the pump that allow to drug to remove outside the device. It is widely employed for veterinary use. In case of animal for the delivery of antibiotics or growth hormones this pump is implanted.

Higuchi-Theeuwes Osmotic Pump¹³:-

During 1970s another variant of the Rose was developed – Nelson pump, is easier than the Higuchi-Leeper pump. In this processes, a rigid house consisted of a

semipermeable membrane. This membrane is stronger to where the pressure developed in the device due to imbibition of water. Drug is loaded in device for long couple of times. Salt chamber is also use.

Elementary Osmotic Pump:-

Osmotic pump is a new delivery system for delivering drugs, agents of which a delivered by osmotic control resides in the:

- Semi permeable membrane possesses water permeable characteristics. Which surrounds the formulating agent.
- Osmotic properties of the formulation

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 within 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.

Push Pull Osmotic Pump:-

Push pull osmotic pump is a modified EOP. At constant rate it can deliver both poorly soluble as well as highly water soluble drugs. It is similar to the bilayer coated tablet in which first layer contain drug in polymeric formulation, osmotic agents and additives. This polymeric osmotic agent can form a suspension of drug in an appropriate position. When this upper layer absorbs water the other layer contains polymeric formulation, osmotic agents and additives. Afterwards all the layers are bind and pressed together to get a single layer. Then coating was applied and then drilling was done.

Osmotic Pump with Non Expanding Second Chamber:-

The multi chamber of second category consists two. First chamber contains of salt and second is used to dilute the drug.

Example:- The problems that lead to withdrawal of osmosis, the device have porous tablet like structure which is helpful in with drawing drug. Before releasing the drug should pass the second chamber. These type of devices further consists two chamber device and is very rigid. First chamber consists sugar and the second chamber contain the main drug¹⁴.

Osmotic Brusting Osmotic Pump:-

This system is similar to an 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 (Liquid Oral Osmotic System) are designed to deliver drugs as liquid formulations and combine the benefits of extended release with high bioavailability. They are of three types: -

- L-OROS hard cap,
- 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, thereby forcing the liquid formulation to be delivered from the delivery orifice. Whereas L-OROS hardcap or softcap systems are 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 1 to 10 hour, depending on the permeability of the rate controlling membrane and thickness of the placebo layer.

Delayed Delivery Osmotic Device:-

Because of their semi permeable walls, an osmotic device 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.

Telescopic Capsule for Delayed Release:-

This device consists of two chambers, the first contains the drug 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.

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. 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 flowable 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):-

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. Thus SOTS can be suitable for drugs prone to cause local irritation of the gastric mucosa.

Monolithic Osmotic System:-

It constitutes a simple dispersion of water-soluble agent in polymer matrix. When the system comes in contact with the aqueous environment. Water imbibitions by the active agent's takes place rupturing the polymer matrix capsule surrounding the drug. Thus liberating it to the outside environment¹⁵.

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. Osmat thus 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.

Controlled Porosity Osmotic Pump:-

It is an osmotic tablet wherein the delivery orifices (holes) are formed in situ through leaching of water soluble poreforming agents incorporated in semipermeable membrane. Drug release rate from CPOP depends on various factors like coating thickness, solubility of drug in tablet core, level of leachable poreforming agent(s) and the osmotic pressure difference across the membrane. There are several obvious

advantages inherent to the CPOP system. The stomach irritation problems are considerably reduced, as drug is released from the whole of the device surface rather than from a single hole.

FACTORS AFFECTING RELEASE OF MEDICAMENT¹⁶:-

Factors affecting the release rate of medicament from osmotic drug delivery system are,

- Solubility
- Osmotic pressure
- Delivery orifice
- Membrane type

Solubility:-

Solubility of drug is one of the most important factors since kinetic of osmotic release is directly related to the drug solubility. The kinetics of osmotic drug release is directly related to the drug solubility within the drug core.

The fraction of a drug release with zero order kinetic is given by

$$F(z) = 1 - S/P$$

Where $F(z)$ = fraction release by zero order

S = drug solubility in g / cm³

P = density of core tablet.

Drug with density of unity and solubility less than 0.05 g / cm³ would release greater than or equals to 95 % by **zero order kinetics**

Drug with density > 0.3 g / cm³ solubility would demonstrate with higher release rate > 70 % by zero order.

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 release rate of a drug from an osmotic system is directly proportional to the osmotic pressure of the core. The simplest and most predictable way to achieve a constant osmotic pressure is to maintain a saturated solution of osmotic agent in the compartment. If a saturated solution of the drug does not possess sufficient osmotic pressure, an additional osmotic agent must be added to the core formulation. The addition of carbonate or bicarbonate salt to the drug chamber offers an advantage since the effervescent action prevents the precipitated drug from blocking the delivery orifice in the tablet.

Delivery orifice:-

Majority of osmotic delivery systems contain at least one delivery orifice (performed 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 the delivery orifice must be smaller than a maximum size S_{max} to minimize drug delivery by diffusion through the orifice. Furthermore, the area must be sufficiently large, above a minimum size S_{min} , to minimize hydrostatic pressure buildup in the system. Otherwise, the hydrostatic pressure can destroy the

membrane and affect the zero-order delivery rate. Therefore, the cross-sectional area of the orifice should be maintained between the minimum and maximum values.

Membrane type:-

Some of the membrane variables that are important in the design of oral osmotic system are:

Type and nature of polymer:-

Any polymer permeable to water but impermeable to solute can be selected. Some of the polymers that can be used for above purpose included Hydroxyl ethylcellulose, carboxy methylcellulose, hydroxyl propyl methylcellulose.

Membrane thickness:-

Thickness of the membrane has a marked effect on the drug release from osmotic system, which is inversely proportional to each other.

Type and amount of plasticizer:-

In pharmaceutical coatings, plasticizers or low molecular weight diluents are added to modify the physical properties and improve film-forming characteristics of polymers. Plasticizers can change viscoelastic behavior of polymers significantly. In particular, plasticizers can turn a hard and brittle polymer into a softer; possibly make it more resistant to mechanical stress. These changes also affect the permeability of polymer films.

Evaluation of Oral Osmotic Drug Delivery Systems¹⁷⁻²³:-

Oral osmotic drug delivery systems can be evaluated for following:

Visual inspection:-

Visual inspection of the film for 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 and 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 vertically reciprocating shaker, conventional USP dissolution apparatus I and II, flow-through apparatus etc.

Effect of pH:-An Osmotically controlled release system delivers its contents independently of external variables. To check this, dissolution media with different pH is used.

Effect of agitation intensity:-

In order to study the effect of agitational intensity of the release media, release studies is carried out in dissolution apparatus at various rotational speeds.

In Vivo Evaluation:-

In vivo evaluation can also be performed in healthy human volunteers. Various pharmacokinetic parameters

(C_{max} , T_{max} , AUC and MRT) and relative bioavailability are calculated.

Conclusion:-

As the system above mentioned and discussed have lot of uses and it is the best method of the delivering drugs. But on the same hand there are some disadvantages to but they can be managed well if taken proper care. There are lot of components and pumps used in this technique which if used with proper care and knowledge can act as boon as this system of delivering drugs are highly accepted and these techniques are very interesting as well as fruitful in the field of drug.

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