REVIEW ON NATURAL PUMPS: A NOVEL DRUG DELIVERY SYSTEM

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ABSTRACT

Pharmaceutical invention and research are increasingly focusing on delivery systems which enhance desirable therapeutic objectives while minimizing the side effects. The conventional dosage forms have less control on the drug release and no control over the effective concentration at the target site. This dosing pattern mostly results in constantly changing, unpredictable plasma concentrations. By the process of osmosis one can deliver the drug in a controlled manner over a long period of time. Osmotic drug delivery systems are most promising systems for controlled drug delivery. These Osmotic devices can be used orally or as implants for the delivery of the active agents. The release of the drugs from the osmotic systems is affected by various formulation factors such as osmotic pressure and solubility of the core component, size of the delivery orifice and nature of the rate controlling membrane. By the optimization of the formulation and processing factors, it is possible to develop osmotic devices to deliver the drugs at a pre-programmed rate mostly zero order release. In present review the focus is on the basic principles of osmosis, history of osmotic pumps, Formulation aspects and Types of osmotic systems with examples and illustrative figures.

Keywords: Principle of Osmosis, Osmotic pumps, Controlled release, Osmogen, Formulation aspects.

INTRODUCTION

In recent years, considerable attention has been focused on the development of novel drug delivery system (NDDS). The reason for this revolutionary shift is relatively low development cost and time required for introducing a NDDS as compared to a new chemical entity. In the form of NDDS, an existing drug molecule can get a 'new life'; there by increasing its market value, competitiveness, and patent life [1].

Oral controlled release (CR) systems continue to be the most popular amongst all the drug delivery systems. Conventional oral drug delivery systems supply an instantaneous release of drugs, which cannot control the release of drug and the effective concentration at target site. The drug bioavailability from these dosage forms or formulations may vary significantly, depending on the several physico-chemical properties of the drug and various excipients, various physiological factors such as the presence or absence of the drug and various excipients, various physiological factors such as the presence or absence of food, pH of the Gastro intestinal tract, GI motility etc. Majority of controlled or modulated drug release design are available to overcome these limitations.

Many of per oral dosage forms fall in the category of matrix, reservoir or osmotic system. Drug release form these systems is independent of pH and other physiological parameter to a large extent and it is possible to modify the release characteristic by optimizing the properties of drug and system, the oral osmotic pumps have certainly came a long way and the available products on this technology and number of patent granted in the last few years makes it presence felt in the market [2].

Drug release from a membrane- reservoir device can also take place through a membrane via an osmotic pumping mechanism. In this case, a semipermeable membrane, such as cellulose acetate, is utilized to regulate osmotic permeation of water. With constant reservoir volume, this type of device delivers a volume of drug solution equal to the volume of osmotic water uptake within any given time interval. The rate of osmotic water influx, and therefore the rate of drug delivery by the system, will be constant as long as a constant thermo dynamic activity gradient is maintained across the membrane However, the rate declines parabolically once the reservoir concentration falls below saturation. Such an osmotic delivery system is

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capable of providing not only a prolonged zero-order release, but also a delivery rate much higher than that achievable by the solution- diffusion mechanism.

Osmotically controlled release is also applicable to drugs with a wide range of molecular weight and chemical composition, which are normally difficult to delivery by the solution- diffusion mechanism. Osmotically controlled drug release requires only osmotic pressure to be effective, and is essentially independent of the environment. As a consequence, this should be an excellent sustained- release system for oral dosage forms. Thus, the drug delivery rate for an oral osmotic therapeutic system can be precisely predetermined regardless of pH changes [3].

Osmotic pressure is a most important colligative property according to pharmaceutical point of view. Colligative property is the concentration of solution independent of solute property. Osmotic pressure of a solution is the external pressure that must be applied to the solution in order to prevent it being diluted by the entry of solvent via a process known as Osmosis.

Such membrane is only permeable to solvent molecule. Because only solvent can pass through the semi-permeable membrane, the driving force the osmosis arises from the inequity of the chemical potential of the solvent on opposing side of the membrane.

Osmotic pressure is used; [4]
(i) For adjustment of tonicity in,
1. Parenteral
2. Ophthalmic
(ii) For developing osmotic drug delivery system
(iii) For oral use in of treatment of,
1. Constipation
2. Hypertension.

Advantages

Osmotic drug delivery systems for oral and injectable use offer distinct and practical advantages over other means of delivery. The following advantages have contributed to the popularity of osmotic drug delivery systems [5].
➢ The delivery rate of zero-order is achievable with osmotic systems.
➢ Delivery may be delayed or pulsed, if desired.
➢ Higher release rates are possible with osmotic system compared with conventional diffusion-controlled drug delivery systems.
➢ The release rate of osmotic systems is highly predictable and can be programmed by modulating the release control parameters.
➢ For oral osmotic systems, drug release is independent of gastric pH and hydro dynamic conditions.
➢ The release from osmotic systems is minimally by the presence of food in gastrointestinal tract.
➢ A high degree of *invivo- invitro* correlation (IVIVC) is obtained in osmotic system.

Limitations
➢ Special equipment is required for making on orifice in the system.
➢ Residence time of the system in the body varies with the gastric motility and food intake.
➢ It may cause irritation or ulcer due to release of saturated solution of drug.
➢ Retrieval therapy is not possible in the case of unexpected adverse events.
➢ If the coating process is not well controlled there is a risk of film effects, which results in dose dumping [6].

Basic Principle Involved In Osmosis

Osmosis is the transport of water across a selectively permeable membrane from a region of higher water chemical potential to a region of lower water chemical potential. It is driven by a difference in solute concentration across the membrane that allows passage of water, but rejects most solute molecules or ions. Osmotic pressure (π) is the pressure which, if applied to the more concentrated solution, would prevent transport of water across the membrane FO (Forward Osmosis) uses the osmotic pressure differential ($\Delta\pi$) across the membrane, rather than hydraulic pressure differential (as in RO), as the driving force for transport of water through the membrane. The FO process results in concentration of a feed stream and dilution of a highly concentrated stream (draw solution) [7].

PRO (Pressure Retarded Osmosis) can be viewed as an intermediate process between FO and RO, where hydraulic pressure is applied in the opposite direction of the osmotic pressure gradient (similar to RO).However, the net water flux is still in the direction of the concentrated draw solution (similar to FO).

The general equation describing water transport in FO, RO, and PRO is;

$$Jw = A(\sigma\,\Delta\pi - \Delta P)$$

Where,
Jw = Water flux,
A = Water permeability
σ = Reflection coefficient
ΔP = Applied pressure
For FO, ΔP is zero; for RO, $\Delta P > \Delta\pi$; and for PRO, $\Delta\pi > \Delta P$.

The flux directions of the permeating water in FO, PRO, and RO are illustrated in Fig 1.

Flux directions and driving forces for the three processes were characterized in the early 1980's by Lee et al. The FO point, PRO zone, and RO zone, along with the flux reversal point, are illustrated in Fig 2.

Draw Solution (Osmogents)

The concentrated solution on the permeate side of the membrane is the source of the driving force in the FO process. Many other terms are used to name this solution that include, osmotic agent, osmotic media, driving solution, osmotic engine, sample solution, or just brine [8].

When selecting a draw solution, the main criteria is that is has a higher osmotic pressure than the feed solution. The osmotic pressures of several solutions being considered for use as draw solution were calculated using OLI Stream Analyser 2.0 (OLI Systems Inc. Morris Plains, NJ) and are presented in Fig 3 as function of molarity.

History of Osmotic Pumps

Nearly 77 years after the discovery of the osmosis principle, it was first used in the design of drug delivery system [9]. Rose and Nelson, the Australian scientist, were initiators of osmotic rug delivery. In 1955, they developed an implantable pump, which consisted of three chambers:

A drug chamber,

A salt chamber contains excess solid salt,

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 pump. The pumping rate of this push-pull is given be the equation;

$$\frac{dM}{dt} = \frac{dV}{dt}\, c$$

In general, this equation, with or without some modification, applies to all other type of osmotic systems.

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 body. 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 is 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 [10].

Further simplified variant of Rose-Nelson pump was developed by Higuchi and Theeuwes. This comprises a rigid rate controlled 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 chamber [11].

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 semi permeable 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 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. This residual dissolved agent continues to be delivered at a declining rate until the osmotic pressure inside and outside the tablet is equal. Normally, the EOP delivers 60-80% of its contents at a constant rate, there is a short lag time of 30-60 min as the system hydrates before zero order delivery from the EOP is obtained.

Formulation Aspects of Osmotic Drug Delivery Systems
The osmotic drug delivery system comprises of [12, 13]
1. The Core, which is made of
- Active drug,
- Fillers,
- Viscosity modifiers,
- Solubilizer,
- Lubricant or Glidant.
2. Coating composed of;
- Polymer,
- Plasticizer,
- Membrane,
- Colour and Opacifier.

[A] Drug
Drug itself may act as an osmogen and shows good aqueous solubility (e.g. potassium chloride pumps). But if the drug does not possess an osmogenic property, osmogenic salt and other sugars can be incorporated in the formulation.
Characteristics of drug candidate for osmotically controlled drug candidate for osmotically controlled drug delivery;
- Short biological half-life(2-6 hr).
- Highly potent drug.
- Required for prolonged treatment e.g. Nefidipine, Glipizide, Verapamil

[B] Omotic Agents
Osmogens used for fabrication of osmotic dispensing device are inorganic or organic in nature a water soluble drug by itself can serve the purpose of an osmogens.
Example: Inorganic water-soluble osmogens.
- Magnesium sulphate
- Sodium chloride
- Sodium sulphate
- Potassium chloride

- Sodium bicarbonate

Organic polymer osmogens;

- Sodium carboxy methyl cellulose,
- Hydroxy propyl methyl cellulose,
- Hydroxy ethyl methyl cellulose,
- Methyl cellulose,
- Poly ethylene oxide,
- Poly vinyl pyrollidine.

[C] Semi Permeable Membrane

The semipermeable membrane should be a stable both to the outer inner environment of the device. The membrane must be sufficiently rigid so as to retain its dimensional integrity during the operational lifetime of the device. The membrane should also be relatively impermeable to the contents of dispenser so that osmogens is not lost by diffusion across the membrane finally, the membrane must be biocompatible.

Ideal Property of Semi-permeable membrane:

The semi-permeable membrane must meet some performance criteria;

- The material must possess sufficient wet strength (-10^5) and wet modulus so as to retain its dimensional integrity during the operational life time of the device.
- The membrane exhibit sufficient water permeability so as to retain water flux rate in the desired range. The water vapour transmission rates can be used to estimate water flux rates.
- The reflection co-efficient 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 agents.
- The membrane should be biocompatible.
- The membrane should also be rigid and non-swelling.
- Should be sufficient thick to withstand the pressure within the device.

[D] Plasticizer

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

- Polyethylene glycols
- Ethylene glycol mono acetate and di-acetate for low permeability.
- Tri ethyl citrate
- Diethyl tartarate or di-acetin for more permeable films.

[E] Hyrophilic and Hydrophobic Polymers

These polymers are used in the formulation development of osmotic systems containing matrix core. The selection of polymer is based on the solubility of drug as well as the amount and rate of drug to be released from the pump.

The highly water soluble compounds can be co-entrapped in hydrophobic matrices and moderately water soluble compounds can be co-entrapped in hydrophobic matrices to obtain more controlled release.

Examples of hydrophilic polymers are hydroxy ethyl cellulose, carboxy methyl cellulose, hydroxyl propyl methyl cellulose, etc.

Examples of hydrophobic polymers are ethyl cellulose, wax material, etc.

[F] Wicking Agents

It is defined as a material with the ability to draw into the porous network of a delivery device. The function of the wicking agent is to draw water to surfaces inside the core of the tablet, thereby creating channels of a network of increased surface area.

Examples:

- Colloidon silicon dioxide,
- Kaolin,
- Titanium dioxide,
- Alumina,
- Niacinamide,
- Sodium lauryl sulphate,
- Low molecular weight polyvinyl pyrrolidone (PVP),
- Bentonite,
- Magnesium aluminium silicate,
- Polyester,
- Polyethylene, etc.

[G] Solubilizing Agnets

Non- swellable solubilizing agents are classified into three groups.

➤ Agents that inhibit crystals formation of the drugs or otherwise act by complexation of drug (example, PVP, PEG, and Cyclodextrin).

➤ A high HLB micelle forming surfactant, particularly anionic surfactants (e.g. Tween 20, 60, 80, polyoxyl ethylene or polyethylene containing surfactants and other long chain anionic surfactants such a SLS).

➤ Citrate esters and their combinations with anionic surfactants (e.g. alkyl esters particularly tri ethyl citrate).

[H] Surfactants

Surfactants are added to wall forming agents. They act by regulation the surface energy of materials to improve their blending into the composite and main their integrity in the environment of use during the drug release period.

Examples:

- Polyoxyethylenated glyceryl recinolate,
- Polyowyethylenated castor oil having ethylene oxide,
- Glyceryl laurates, etc.

[I] Coating Solvents

Solvents suitable for making polymeric solution that is used for manufacturing the wall of the osmotic device include inert inorganic and organic solvents.

Examples:

- Methylene chloride,
- Acetone,
- Methanol,
- Ethanol,
- Isopropyl alcohol,
- Ethyl acetate,
- Cyclohexane, etc.

[J] Flux Regulators

Flux regulating agents or flux enhancing agent or flux decreasing agents are added to the wall forming material; it assist in regulating the fluid permeability through membrane.

Poly hydric alcohols such as poly alkylene glycols and low molecular weight glycols, such as poly propylene, poly butylene, and poly amylene can be added as flux regulators.

[H] Pore Forming Agents

These agents are usually used in the pumps developed for poorly water soluble drug and in the development of controlled porosity or multi-particulate osmotic pumps.

The pore formers can be inorganic or organic and solid or liquid in nature.

Like,

- Alkaline metal salts such as sodium chloride, sodium bromide, potassium chloride, etc.
- Alkaline earth metals such as calcium chloride and calcium nitrate.
- Carbohydrates such as glucose, fructose, mannose, etc.

Types of Osmotic Pumps

[I] Implantable Osmotic Pumps
1. Rose-Nelson Pump
2. Higuchi Theeuwes pump
3. Mini Osmotic pump
4. Higuchi- Leeper pump

[II] Oral Osmotic Pumps
1. Elementary Osmotic pump
2. Controlled porosity osmotic pump
3. Modified osmotic pump
4. Multi-particulate delayed release system
5. Monolithic osmotic system
6. Multi chamber osmotic pump
(i) Non- expandable
(ii) Expandable
(a) For liquid osmotic system
(b) For solid osmotic system
- Bilayer
- Tri layer

[I] IMPLANTABLE OSMOTIC PUMPS
1. Rose-Nelson Pump

In the year 1955, these two Australian physiologists reported the first osmotic pump to the gut of sheep and other cattle. The pump is constructed of three chambers viz., a drug chamber with an orifice, a salt chamber with elastic diaphragm containing excess solid salt, and a water chamber. A semipermeable membrane separates the drug and water chamber. The difference in osmotic pressure across the membrane moves water from the water chamber into the salt. The volume of chamber increases because of this water flow, which distends the latex diaphragm separating the salt and drug chambers, there by pumping drug out of the device [14].

2. HIGUCHI-THEEUWES PUMP

In the early 1970 Higuchi-Theeuwes developed a similar form of Rose-Nelson pump as shown in the figure 8. The semipermeable wall itself acts as a rigid outer casing of the pump. The device is loaded with drug prior to use (Vyas et al, 2001). When the device is put in an aqueous environment the release of the drug follows a time course set by the salt used in the salt chamber and the permeability of the outer membrane casing [15].

3. MINI OSMOTIC PUMPS

Mini osmotic implantable pumps were initially designed by Alza Corp. for experimental studies in animal models.

These pumps operate on 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 semipermeable 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 [16].

4. HIGUCHI- LEEPER PUMP

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 body. 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 be the production of a critical pressure at which the delivery orifice opens and releases the drug [17].

[II] ORAL OSMOTIC PUMPS
1. ELEMENTARY OSMOTIC PUMPS

The basic OROS system, the elementary osmotic pump (EOP), was first described by Theeuwes in 1975. It consists of a drug containing core, a semipermeable membrane made of water-permeable cellulose polymers, and orifices from drug release. Water is drawn into the system by osmosis, displacing drug in the core, which is them released through the orifices [18].

The release profile of an EOP system declines when solid drug in the core is depleted; therefore, a drug with high solubility cannot maintain prolonged zero order release. A drug with low solubility, however, lacks the ability to generate sufficientosmotic pressure, leaving moderately soluble drugs as the most appropriate for the EOP system.

Normally EOP deliver 60-80 % of its content at constant rate. It has short lag time of 30-60 minutes.

2. CONTROLLED POROSITY OSMOTIC PUMP

This system comprises an inner core compartment of osmotically active composition surrounded by an enclosing wall material. The core comprises pharmacologically active agents soluble in an external fluid, or a mixture of agents having a limited solubility in the external fluid with osmotically effective solutes that are soluble in the fluid, which exhibit an osmotic pressure gradient across the wall against the external fluid. The wall constitutes a layer of controlled porosity that is substantially permeable to both the external fluid and the core composition. Agents is released from the system by fluid imbibition through the wall into the inner core compartment at a rate controlled by the wall composition and dimensions, producing a solution containing agent that is released through the wall at a controlled rate in response to fluid volume flux, dv/dt, resulting from the osmotic pressure gradient, and diffusive flux, $(dM/dt)_D$, driven by the chemical potential gradient of the agent across the wall. The total rate of agent release, $(dM/dt)_T$, is given by equation below where C is the concentration of the active agent in the dissolve core composition an remains constant when excess solid core mass is present. [19]

$$\left[\frac{dM}{dt}\right]_T = \left[\frac{dV}{dt}\right]_{(D)} + \left[\frac{dM}{dt}\right]_D$$

3.MULTIPARTICULATE DELAYED RELEASE SYSTEMS

Multiparticulate drug delivery system mainly consists of a multiplicity of small discrete units, each exhibiting some desired characteristics. In these systems, the dosage of the drug substances is divided on a plurality of subunit, typically consisting of thousands of spherical particles with diameter of 0.05-2.00 mm. Thus multiparticulate dosage forms are pharmaceutical formulations in which the active substance is present as a number of small independent subunit. To deliver the recommended total dose, these subunits are filled into sachets and encapsulated or compressed into a tablet [20].

4.MONOLITHIC OSMOTIC SYSTEMS

It constitutes a simple dispersion of water-soluble agent in polymer matrix. When the system comes in contact with the aqueous environment, water imbibition by the active agents takes place rupturing the polymer matrix capsule surrounding the drug, thus liberating it to the outer environment of the polymeric matrix, but gradually proceeds towards the interior of the matrix in a serial fashion. However this system fails if more than 20-30 volume per litre of the active agents is incorporated into the device as above this level, significant contribution from the simple leaching of the substance takes places [21].

5.MULTICHAMBER OSMOTIC PUMPS
(i) Non expandable multichamber osmotic pump
This group can be subdivided into two sub groups depending upon the function of the second chamber.

➢ In one group the second chamber serves for the dilution of the drug solution leaving the device. This is important in cases where drug causes irritation of Gastrointestinal Tract.

➢ Before the drug can exit from the device, it must pass through a second chamber. Water is also drawn osmotically into this chamber either due to osmotic pressure of the drug solution or because the second chamber that bears water-soluble diluents such as sodium chloride [22].

➢ The second group of non- expandable multi chamber devices essentially contains two separate simple OROS tablets formed into a single tablet. Two chambers contain two separate drugs both are delivered simultaneously. This system is also known as sandwiched osmotic tablet system. (SOTS)

A more sophisticated version of this device consists of two rigid chambers, one contains biologically inert osmotic agent such as sugar or Nacl, and the second chamber contains the drug. When exposed to aqueous environment, water is drawn into both chambers across the semipermeable membrane. The solution of osmotic agents then passes through the connecting hole and where it mixes with drug before escaping through the micro porous membrane, that form a wall around the drug chamber. Relatively insoluble drugs can be delivered through this device.

(ii)Expandable multichamber osmotic pump
In the devices with a second expandable osmotic chamber, the water is simultaneously drawn into both the chambers in proportion to their respective osmotic gradient, eventually causing an increase in volume of the chamber and subsequently forcing the drug out from the drug chamber.

The matrix should have sufficient osmotic pressure to draw water through the membrane into the drug chamber. Under hydrated condition matrices should have to be pushed easily through a small hole by the little pressure generated by the elastic diaphragm.

OROS® technology employs osmosis to provide precise, controlled drug delivery for up to 24 hours and can be used with a range of compounds, including poorly soluble or highly soluble drugs [23].

LIQUID OSMOTIC SYSTEM (L-OROS)
➢ A liquid formulation is particularly well suited for delivering insoluble drugs an macromolecules such as polysaccharide and polypeptides [24].
➢ Such molecules require external liquid components to assist in solubilisation, dispersion, protection from enzymatic degradation and promotion of gastrointestinal absorption.
➢ Thus, the L-OROS system was designed to provide continuous delivery of liquid drug formulation and improve bioavailability of drugs.
➢ Another type of L-OROS system consists of a hard gelatin capsule containing a liquid drug layer, a barrier layer

and a push layer surrounded by a semipermeable membrane. The L-OROS hardcap system was designed to accommodate more viscous suspensions with higher drug loading than would be possible using softcap design.

LIQUID DRUG DELIVERY OTHER THAN L-OROS
Use of porous particle;
➢ The controlled release of liquid active agent formulation is provided by dispersing porous particle that contain the liquid active agent formulation in osmotic push-layer dosage forms.
➢ The liquid active agent formulation may be absorbed into the interior pores of the material in significant amounts and delivered to the site of administration in the liquid state.
➢ Microcrystalline cellulose, porous sodium carboxy methyl cellulose, porous soya bean fibre and silicon dioxide- all of which have high surface area and good absorption properties and can be used in dosage form [25].

Table 1. List of Osmotic drug delivery systems in market with their dosage and use:

Trade Name	Active Ingredient	Design system	Dose	Use
Alpress I.P	Prazosin	Push-Pull	2.5- 5mg	For the treatment of Hypertension
Acutrim	Phenylpropanol amine	Elementary Pump	75 mg	For the treatment of congestion associated with allergies, hay fever, sinus irritation, and the common cold.
Cardura XL	Doxazosin	Push- Pull	4, 8 mg	For the treatment of Hypertension
Covera HS	Verapamil	Push- Pull with time delay	180, 240mg	Management of Hypertension and Angina
Ditropan XL	Oxybutinin chloride	Push- Pull	5, 10 mg	For the once daily treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency.
Dynacirc CR	Isradipine	Push- Pull	5, 10 mg	For the treatment of Hypertension
Invega	Paliperidone	Push- Pull	3, 6, 9 mg	For the treatment of Schizophrenia
Efidac 24	Chlorpheniramine maleate	Elementary pump	4 mg IR, 12mg CR	Antihistamine Chlorpheniramine is used to treat sneezing; runny nose; itching, watery eyes; hives; rashes; and other symptoms of allergies and the common cold.
Glucotrol XL	Glipizide	Push- Pull	5, 10 mg	For the control of Hyperglycemia in diabetic patients.
Minipress XL	Prazocine	Elementary Pump	2.5, 5 mg	Antihypertensive Agent
Procardia XL	Nifedipine	Push- Pull	30, 60, 90mg	Calcium channel blocker. It is used to treat high blood pressure and chest pain (angina).
Sudafed 24	Pseudoephedrine	Elementary Pump	240 mg	Pseudoephedrine is used for the temporary relief of stuffy nose and sinus pain/pressure caused by infection or other breathing illnesses.
Volmax	Salbutamol	Elementary Pump	4, 8 mg	For relief of bronchospasm in patients with reversible obstructive airway disease.
Tegretol XR	Carbamazepine		100, 200, 400 mg	For use as an anticonvulsant drug
Viadur	Leuprolide acetate	Implantable osmotic systems		
Chronogesic	Sufentanil	Implantable osmotic systems		Anaesthetics, Intravenous; Narcotics; Adjuvants, Anaesthesia; Analgesics, Opioid; Opiate Agonists
Concerta	Methylphenidate	Implantable osmotic systems	18, 27, 36 and 54 mg	A psycho-stimulant drug approved for treatment of attention- deficit hyperactivity disorder, Postural Orthostatic Tachycardia Syndrome, and narcolepsy.

Fig 1. Solvent flow in FO, PRO and RO. For FO, ∆P is approximately zero and water diffuses to the more saline side of the membrane. For PRO, water diffuses to the more saline liquid that is under positive pressure (∆π > ∆P). For RO, water diffuses to the less saline side due to hydraulic pressure (∆P > ∆π).
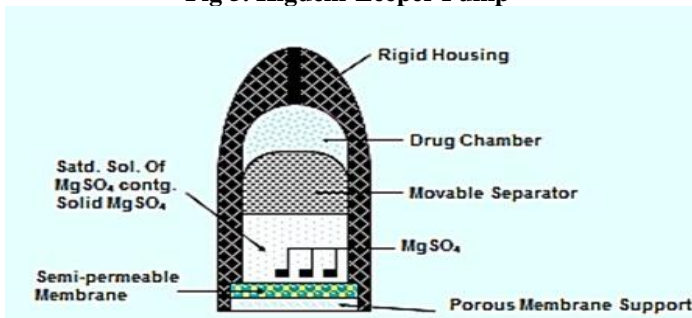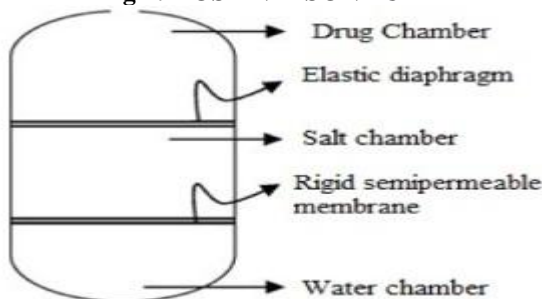

Fig 2. Direction and magnitude of water flux as a function of applied pressure in FO, PRO, and RO. FO takes place when the hydraulic pressure difference is zero. The PRO zone is where the applied pressure difference is between zero and flux reversal point, and the RO zone is where the applied pressure difference is greater than the osmotic pressure difference.

Fig 3. Osmotic pressure as a function of solution concentration at 25°c for various potential draw solutions. Data were obtained by OLI Stream Analyser 2.0
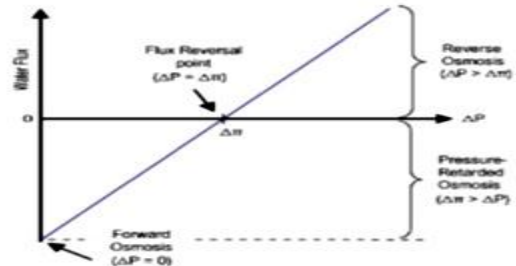
Figure 4. Rose – Nelson Pump

Fig 5. Higuchi-Leeper Pump
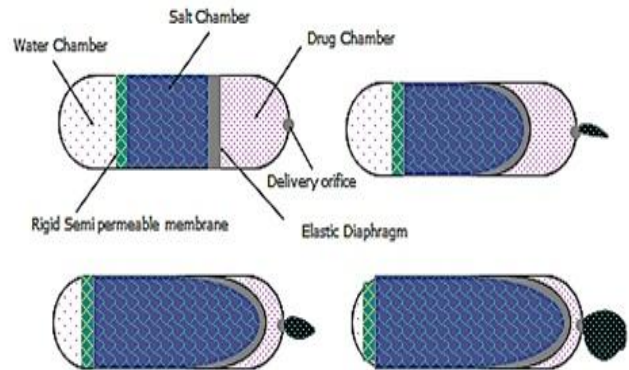
Figure 6. Theeuwes Miniature Osmotic Pump

Fig 7: ROSE NELSON PUMP
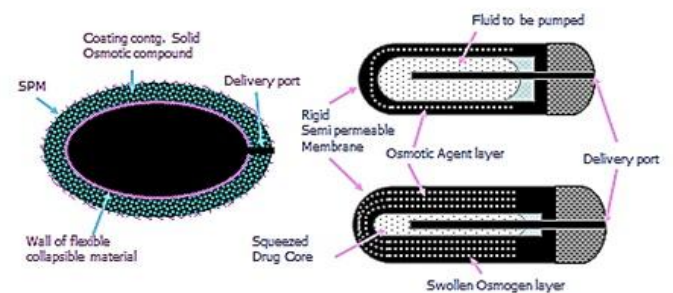
Fig 8. Higuchi Theeuwes Pump
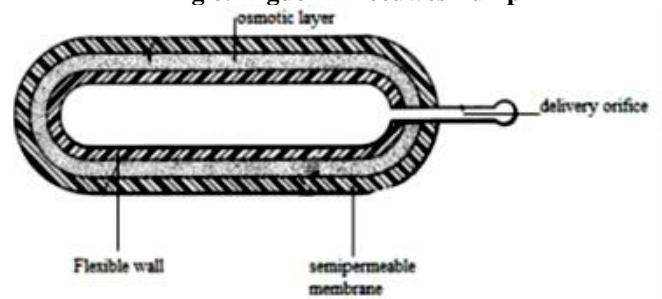
Fig 9. Alzet Mini Osmotic Pumps

Fig 10. Higuchi-Leeper Pump
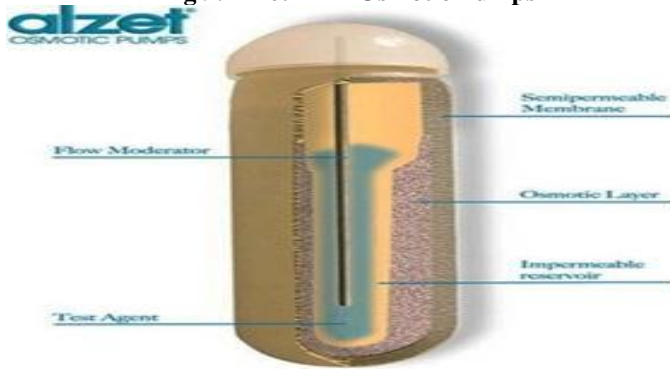
Fig 11. Elementary Osmotic Pump

Fig 12: CONTROLLED POROSITY OSMOTIC PUMP
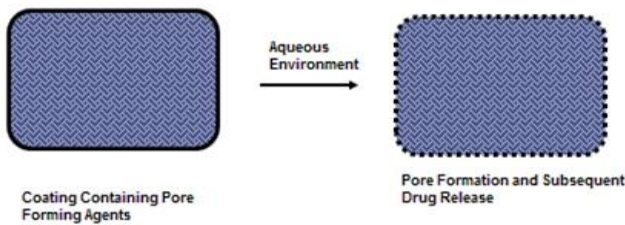
Fig 13. Intestinal Protective Drug Absorption System

Fig 14. Spheroidal Oral Drug Absorption System
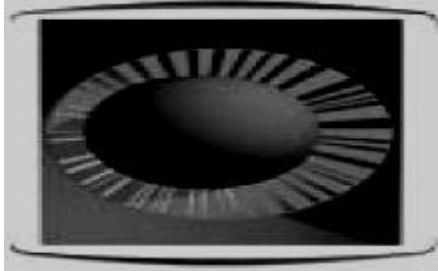
Fig 15. Programable Oral Drug Absorption System

Fig 16. Diffucaps

Fig 17. Minitab

Fig 18. Monolithic Osmotic System
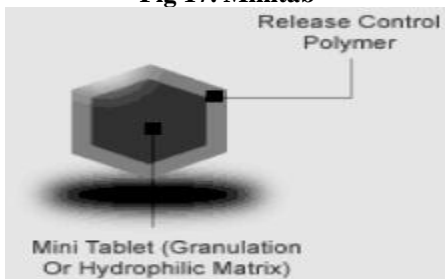
Fig 19. Non Expandable Multichamber Osmotic Pump

Fig 20. Sandwiched Osmotic Tablet System. (SOTS)
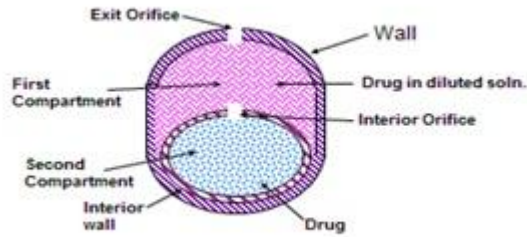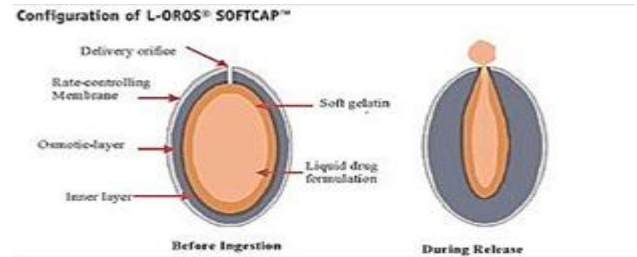
Fig 21. Expandable

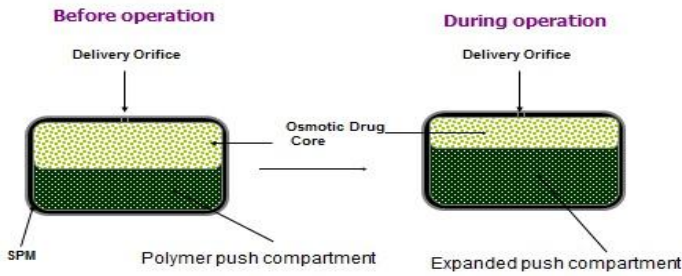**Fig 22. Osmotic Release Oral System (OROS)**

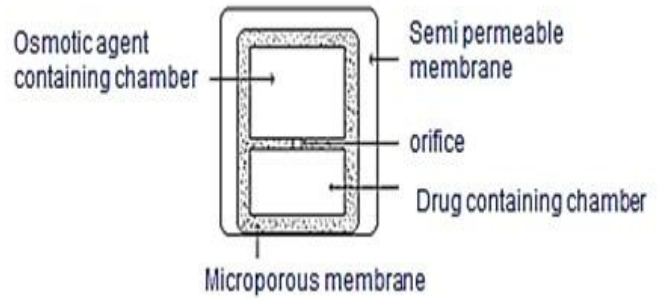**Fig 23.Configuraton of L-Oros Softcap**
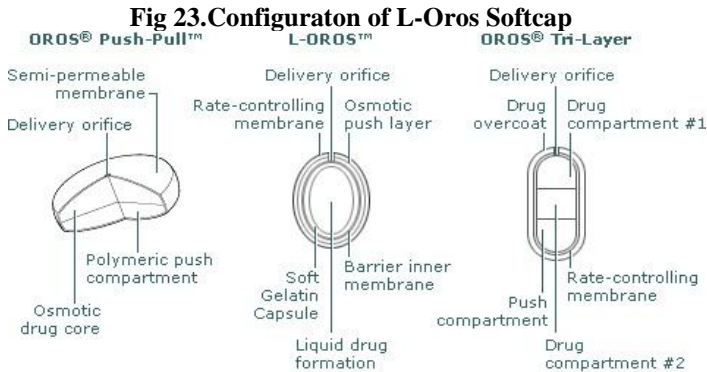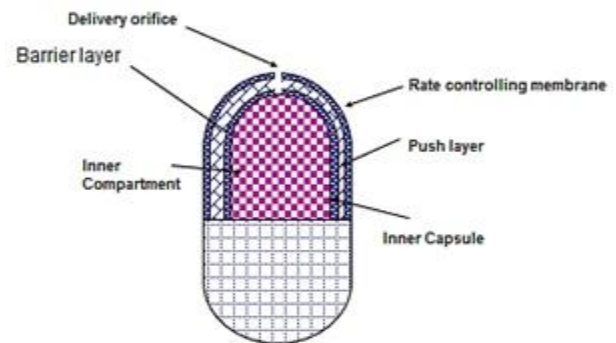
Fig 24. Configuraton of l-oros hardcap

Fig 25. Liquid Drug Delivery Other Than L-Oros

CONCLUSION

The drug delivery systems have become advanced in recent years. In this era of modern science and technology Novel drug delivery systems has been an attractive and recognized drug delivery system for the pharmaceutical and health industry. Among all various NDDS, Osmotic drug delivery system has been evolved as the most reliable controlled release system for animal and humans.

The conventional dosage forms have less control over the drug release an no control over the effective concentration at the target site, whereas, the osmotic drug delivery system can deliver the drug at a pre-programmed rate which results in predictable plasma concentration. With the help of osmotic system the drug can be easily targeted to specific site.

The future of Osmotic drug delivery system as Novel drug delivery system is very promising, which can replace the existing market of conventional dosage form i.e., tablets and capsules, because of its more advantages over the conventional dosage forms. The major advantages include precise control of zero-order or other patterned release over an extended time period—consistent release rates can be achieved irrespective of the environmental factors at the delivery site. Controlled delivery via osmotic systems also may reduce the side-effect profile by moderating the blood plasma peaks typical of conventional (e.g., instant release) dosage forms.

Besides oral osmotic delivery systems, implants that work on osmotic principles are promising for delivery of a wide variety of molecules with a precise rate over a long period of time. Further, with the discovery of newer and potent drugs by the biotechnology industry, the need to deliver such compounds at a precise rate certainly will pave the way for osmotic delivery systems to play an increasingly important role in drug delivery.

REFENENCE

1. Rajan K V *et al.,* Formulation aspects in the development of osmotically controlled oral drug delivery system. *J Cont Rel.,* 79, 2002, 7-27.
2. Harnish P *et al.,* A review on osmotic drug delivery systems. *Ind Res J Pharm.,* 3(4), 2012, 88-94.
3. Vasant VR and Mannfred AH. Drug delivery systems, 2nd Edition, CRC Press, 10, 11.
4. Kaushal AM, Garg S. An update on osmotic drug delivery patents. *Pharma Tech*, Aug 2003: 38-44.
5. Bhatt PP. Osmotic drug delivery systems for poorly soluble drugs. The drug delivery companies report autumn/winter, 2004.
6. Brahma PG, Navneet T, Nishi PJ, Jitendra B, Surendara J. Osmotically controlled drug delivery System with Associated Drugs. *J Pharma Sci*, 13(3), 2010, 571-588.
7. http://www.olisystems.com
8. Stuti G, Ravindra Pal S, Rohitashva S, Renu K and Priyanka L. Osmotic Pumps: A review. *Pharmacie GlobaleInt J Comp Pharma*, 6(1), 2011, 1-8.
9. Lee KL, Baker RW, Lonsdale HK. Membranes for power generation by pressure- retarded osmosis. *J Mem Sci*. 8, 1981, 141- 171.
10. www.pharmainfo.com
11. Tzahi YC, Amy E. Childress, Menachem Elimelech. Forward Osmosis: Principles, application and recent developments. *Science Direct J of Membrane Sci,* 281, 2006, 70-87.
12. www.pharmaquest.com
13. Theeuwes F. Elementary Osmotic Pump. *J Pharm Sci*, 64, 1975, 1987-1991.
14. Higuchi T, Leeper HM. Improved osmotic dispenser employing magnesium sulphate and Magnesium chloride. US Patent 3760804, 1973.
15. Higuchi T, Leeper HM. Osmotic dispenser with means for dispensing active agents responsive to osmotic gradient. US Patent 3995631, 1976.
16. Pandey S, *et al.*, Osmotic Pump drug delivery devices: Form implant to sandwiched oral therapeutic system. *Int J Pharmatech,* 2(1), 693-699.
17. Tanmay G, Amitava G. Drug delivery through osmotic system: A overview. *JAppl Pharm Sci.,* 1(2), 2011, 38-49.
18. Theeuwes F and Yum SI. Principles of the design and operation of generic osmotic pumps for delivery of semi-solid or liquid drug formulation. *Arm Biomed Eng,* 4(4), 1976, 343-353.
19. Zentner, *et al.,* Controlled porosity osmotic pump. US Patent, 4968507, 1990.
20. NS Dey, Majumdar S and MEB Rao. Multiparticulate Drug Delivery Systems for Controlled Release. *Tropical Journal of Pharmaceutical Research*, 7(3), 2008, 1067-1075.
21. Sharma NS and Vyas SK, Jain NK. In: Advanced in controlled and Novel drug delivery, CBS publisher, 28-29.
22. Deeoaj S, Hari Kumar SL and Nirmala. Osmotic pump drug delivery: A novel Approach. *Int J Res Pharm & Chem*, 2(2), 2012, 661-670.
23. Michael JR, Jonathan H, Michael SR. Modified release drug delivery technology, MARCEL DEKKER, INC. New York, BASEL, 105.
24. Parmar NS and Vyas SK. In: Advance in controlled and novel drug delivery, CBS publisher 2008, 28-29.
25. Verma R, Mishra B and Garg S. Osmotically controlled oral drug delivery. *Drug Development and Industrial Pharmacy*, 26(7), 2000, 695-708