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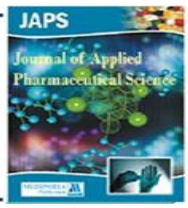

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DRUG DELIVERY THROUGH OSMOTIC SYSTEMS – AN OVERVIEW

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ABSTRACT

The immediate release conventional dosage form lack in the efficiency of controlling the proper plasma drug concentration. This results in the development of various controlled drug delivery system. Among which the Pulsatile drug delivery systems (PDDS)/ osmotic drug delivery system (ODDS) are gaining importance as these systems deliver the drug at specific time as per the path physiological need of the disease, resulting in improved patient therapeutic efficacy and compliance. They work on the principle of osmotic pressure for controlling the delivery of the drug. The release of the drug is independent of physiological factors of the GIT to a large extent. This review highlights' the theoretical concept of drug delivery, history, types of oral osmotic drug delivery systems, factors affecting the drug delivery system, advantages and disadvantages of this delivery systems ,theoretical aspects, applications, marketed status and last but not the least the recent development.

***Key words**:* Osmotic drug delivery system, Osmotic pressure controlled formulation, Pulsatile drug delivery systems, and Sandwich osmotic system.

INTRODUCTION

In the field of medicine and agriculture it is often describe to maintain an effective concentration of an active agent e.g. a pesticides, herbicides, fertilizer or drug at some site of action for prolonged period .One method of achieving this goal is to deliver a large excess of agent so that even though it is metabolized, excreted or degraded sufficiently remains to maintain the effective dose (Chein,1982; Chein, 2005; Joseph et al, 2005). This approach is not only wasteful of active agent but maintaining the effective dose. This approach is not only wasteful of active agent but maintaining such large excess during early portion of delivery period often lead to over dose-related side effects. A better pattern of delivery is to dispense the agent from a sustained release delivery system, which releases the active agent at a slow rate, throughout the delivery period. Recently, several technical advancement has been made. They have resulted in the development of new techniques for drug delivery. These techniques are:

1. Capable of controlling rate of drug delivery.
2. Sustain the duration of therapeutic activity.
3. Targeting he delivery of drug to tissues.

These advanced technique have lead to the development of several **Novel Drug Delivery Systems (NDDS)** which have brought revolution in the method of medication and therapeutic benefit .This also create a confusion in the terminology between controlled release (CR) and sustained release (SR).

Classification of rate controlled drug delivery system (Chein, 2005)

1. Rate pre-programmed drug delivery system.

1. Activation modulated drug delivery system.
2. Feed back regulated drug delivery system.
3. Site specific drug delivery system.

Activation modulated drug delivery system

In this group of CRDDS the release of drug molecule from the drug delivery system is activated by some physical, chemical, or biochemical processes.

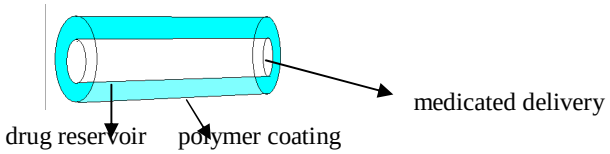

Figure 1

Classifications (Y.W Chein, 2005)

1. **Physical mean**

a. Osmotic pressure activated drug delivery system.
b. Hydrodynamic pressure activated drug delivery system
c. Vapour pressure activated drug delivery system
d. Mechanically activated drug delivery system
e. Magnetically activated drug delivery system
f. Sonophoresis activated drug delivery system
g. Ionotrophoresis activated drug delivery system
h. Hydration activated drug delivery system

2. Chemical means

a. pH activated drug delivery system.
b. Ion exchange drug delivery system.
c. Hydrolysis activated drug delivery system.

3. Biochemical means
a. Enzyme activated drug delivery system.
b. Biochemical activated drug delivery system.

1 a.**Osmotic pressure activated drug delivery system**

This invention relates to an osmotic dispenser and more especially to an osmotically dispenser capable of releasing drug or active ingredient tom its outside environment, at an osmotically controlled rated over a prolonged period of time (Chein, 2005). **ALZA** Corporation pioneered the development of osmotic drug delivery systems. They deliver the drug at a zero-order profile (Chein, 1989).

An osmotically dispersion formulation (Fig.2) comprises of:

1. A water permeable membrane forming a part or all the walls of enclosure surrounding
2. An activated agent.
3. An additive known as an osmotically attractant which together exhibit an osmotic pressure.

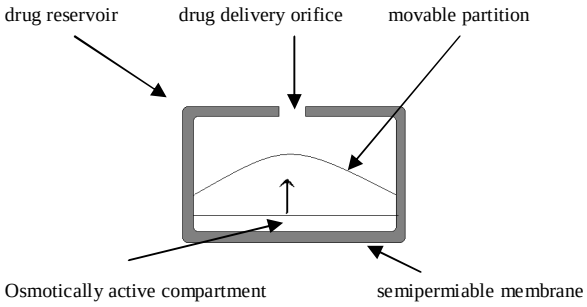

Figure 2

When placed in aqueous environment water is osmotically drawn into the enclosure by the combination action of active component and movable partition which distend and swells and result in the release of drug from the orifice to the external environment. The rate of drug release is modulated by the controlling the gradient of osmotic pressure. The intense rate of drug release **(Q/t)** is defined by:

$$\mathbf{Q/t = \frac{Pw\ Am}{hm}\ (\pi s - \pi c)} \quad \text{---------- (1)}$$

Where:
Pw = water permeability.
Am = effective surface area.
hm = thickness of the semi permeable housing.
($\pi s - \pi c$) = difference of osmotic pressure between the drug delivery system with osmotic pressure (πs) and environment with osmotic pressure (πc)

For the drug delivery system containing a solid formulation the intrinsic rate of drug release should be constant and is define by:-

$$\mathbf{Q/t = \frac{Pw\ Am}{hm}\ (\pi s - \pi c)} \quad \text{---------- (2)}$$

Where
Sd = aqueous solubility e.g.:- Acutrim tablet

Historic back ground

The Rose Nelson pump (Vyas et al, 2001)

In 1955 two Australian physiologist Rose and Nelson reported the first osmotic pump (Fig.3). They were interested in delivery of drugs to the gut of sheep and cattle.

- A drug chamber with an orifice.
- A salt chamber with elastic diaphragm containing excess solid salt.
- A water chamber.

The drug and water chamber are separated by a rigid semi permeable membrane. The difference in osmotic pressure across the membrane moves water from the water chamber into salt chamber. The volume of the salt chamber increases because of

this water flow, which distends the latex diaphragm separating salt and drug chamber there by pumping drug out of this device. The pumping rate of Rose-Nelson pump is given by the equation:

dm/dt = dv/dt *c ---------- (3)

Where:
dm/dt = Drug release rate.
dv/dt = Volume flow of water into salt chamber.
c = Concentration of drug into drug chamber.

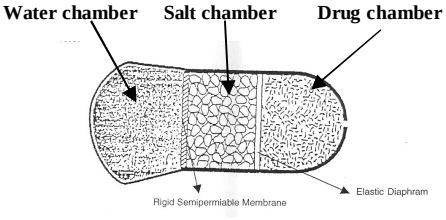

Figure: 3

Higuchi Leeper pump (Vyas et al, 2001)

The design of Higuchi Leeper pump described in the (fig.4) represents the first simplified version of the Rose Nelson pump made by the Alza Corporation in the early 1970. The benefit of this pump 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 is first prepared and then loaded with the drug and then store for weeks or months prior to use.

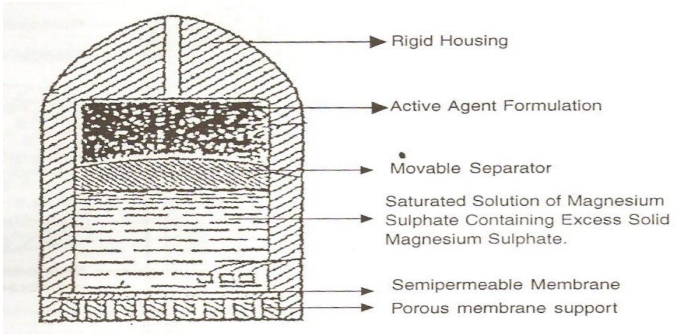

Figure: 4

Higuchi- Theeuwes pump

In the early 1970 Higuchi – Theeuwes developed a similar form of Rose Nelson pump as shown the figure 5. The semi permeable wall itself act 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.

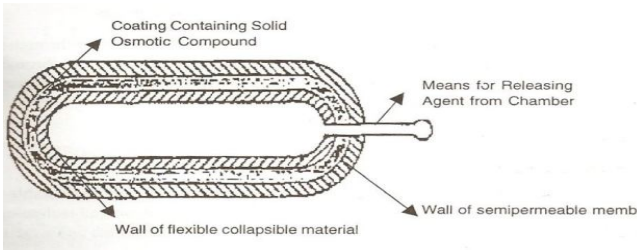

Figure: 5

Table No: 1

Year	Comment	Ref
1748	First report of osmosis	(Banker, 1987).
1877	Quantitative measurement of osmotic pressure	(AMartin.,1993)
1955	First osmotic pump by Rose-Nelson developed pump for pharmaceutical research	(Rose etal,1995)
1973	Higuchi- Leeper introduced a new version of Rose-Nelson pump with certain modification	(Santus et al,1995)
1973	Osmoticaly powdered agent dispense device with filling means.	(Theeuwes,1984)
1975	Introduced the first oral osmotic pump i.e. EOP. It was the major the major mile stone in the field of oral osmotic drug delivery system.	(Cortese et al,1982)
1976	Patent granted on the design of Alzet osmotic pumps which later extensively used as an experimental research tool in laboratory animal.	(Theeuwes et al, 1984)
1979	Osmotic bursting drug delivery device.	(Chein et al,1984)
1982	Patent issue for an osmotic system which consist of a layer of a fluid swell able hydro gel to deliver insoluble to very insoluble to very insoluble drug.	(Corteses, et al,1984)
1984	First report of combination therapy by use of push pull osmotic pump.	(Theeuwes et al, 1984)
1985	Controlled porous osmotic pump was developed from which drug is leached out from the coating, eliminating the need of complicated laser drill procedure.	(Zentner et al, 1991)
1986	Patent issue claiming a delivery system for controlled administration of drug to ruminants.	(Mishra et al, 2006)
1989	Developed of Push Pull osmotic pump of Nefedipine (Procardia XL) by Pfizer which was the largest selling cardiovascular product in US market until 1995	(Mishra et al, 2006) (Wilson et al,2000)
1995	Patent to an osmotic dosage form for liquid drug delivery .The system consist of an outside semi permeable wall, middle osmotic active layer, capsule containing an active agent and an orifice for delivery of the agent.	(Mishra et al, 2006)
1999	Asymmetric membrane capsule is introduced to deliver the drug through the osmotic pressure.	(Mishra et al, 2006)

2000	DUROS Leurpolid implants i.e. Viadur approved as first implantable osmotic pump for human by US FDA.	(Mishra et al, 2006)
2001	Patent granted for dosage form comprising liquid drug formulation that can self emulsify to enhance the solubility, dissolution, & bioavailability of drug.	(Mishra et al, 2006)
2003	First report osmotic floating system.	(Mishra et al, 2006)

Theoretical Aspect

The polymer membrane is not only semi permeable in nature but is also rigid and capable of maintaining the structural integrity of he gastrointestinal delivery system during the course of drug release because of its semi permeable nature, it is permeable to the influx of water in the gastrointestinal tract, on the other hand it is permeable to drug solute. When it is in use, water is continuously get absorbed into the drug reservoir compartment through the semi permeable membrane to dissolve the osmotically active drug and/or salt .A gradient of osmotic pressure is thus created, under which the drug solute are continuously pumped out over a prolonged period of time through the delivery orifice at a rate define by the following equation

$$\mathbf{Q/t = \frac{Pw\ Am}{hm}\ (\pi s - \pi c)\ Sp} \text{ ---------- (4)}$$

Where

Pw = Water permeability**.**

Am = Effective Surface area**.**

hm = Thickness of the semi permeable membrane.

πs = Osmotic pressure of the saturated solution of the osmotic ally active drug or salt**.**

πc = Osmotic pressure of G.I. Fluid**.**

Sp = Solubility of the drug.

The equation 4 follows zero order drug release from the OPCDDS.

In represent to the equation 4 a non zero order release patter can be described by the equation no 5

$$\mathbf{dQ/dt = \frac{(Q/t)\ z}{\{[1+ (Q/t)\ z / Sd\ vt]\ (tr-tz)\}^2}} \text{ ---------- (5)}$$

Where

(Q/t) z = Zero order drug release**.**

vt = Total volume of the drug reservoir compartment.

tz = Total time length in which the system delivers the drug at a zero order rate.

tr = Duration of residence time.

The rate of drug release can further be explain by the help of the Rose Nelson equation as given below

$$\mathbf{dm/dt = A/h\ Lp\ (\sigma\Delta\pi - \Delta p)c} \text{ ---------- (6)}$$

where

dm/dt = Solute delivery rate

As the delivery orifice increases, hydrostatic pressure inside the system is minimized as expressed by the condition $\Delta\pi > \Delta p$ .When the osmotic pressure of the formulation (π) is larger compared to the osmotic pressure of the environment π can be substituted from the equation no6 then it can be reduced to much similar expression in which the constant K replaces the Lp^{σ} so we get

$$\mathbf{dm/dt = A/h\ K\pi C} \text{ ---------- (7)}$$

In case of zero order drug delivery rate the release rate from the elementary osmotic pump is zero when t=0 until a time tz at which the time all the solid in the core has dissolved and it is described by

$$\mathbf{(\ dm/dt)\ z = A/h\ K\pi sS}$$

Where

S = solubility

πs = Osmotic pressure at a saturation.

Nonzero order drug release rate :- The non zero order drug release rate from the system (e.q.7) is obtained by the describing the concentration as the rate of time .For simplification the volume flush into the system is replaced by the symbol F:

$$F = A/h\ K\pi \text{ ---------- (9)}$$

The non zero order release rate can also be explain by the help of the following e.q

$$dm/dt = \frac{(dm/dt)\ z}{[1+1/SV\ (dm/dt)\ z\ (t- tz)]\ 2} \text{ ------- (10)}$$

Advantages (Mishra et al, 2006; Bhatt, 2004)

There are various no of advantages of OCODDS which have been listed below:-

- Decrease frequency of dosing.
- Reduce the rate of rise of drug concentration in the body.
- Delivery may be pulsed or desired if required.
- Delivery ratio is independent of pH of the environment.
- Delivery is independent of hydrodynamic condition, this suggest that drug delivery is independent of G.I. motility.
- Sustained and consistence blood level of drug within the therapeutic window.
- Improve patient compliance.
- High degree of in vitro- in vivo correlation is obtained in osmotic system.
- Reduce side effect.
- Delivery rate is also independent of delivery orifice size within the limit.

Disadvantage & limitation (Bhatt, 2004; Vyas, 2001)

OCODDS have produced significant clinical benefit in various therapeutic areas .Some system have enhanced patient compliance, while other has minimized the side effect of their active compounds. However some limitations of OCODDS have been reported.

- Slightly higher cost of good than matrix tablet or multi particulates ion capsule dosage form.
- Gastro intestinal obstruction cases have been observed with the patient receiving Nifedipine GITS tablet.
- Another case was reported for osmosin (Indomethacin OROS) which was first introduced in the United Kingdom in 1983 .A few month later after its introduction frequent incidences of serious gastrointestinal reaction was observed leading to osmosin withdrawal. Various explanations were given based on the toxic effect of KCl used in osmosin.
- Magnetic resonance imaging (MRI) of tablet elucidate that nonuniform coating leads to different pattern of drug release among the batches.

Some reports from literature on osmotic pump:

Theeuwes and co worker(Theeuwees et al,1983) fabricated EOP of sodium indomethacine trihydrate with release rate of 7,8 and 12mg/hr .They used KHCO3 as osmotic agent due to high osmotic pressure and buffer capacity and coated the system using an air suspension coater. In vitro release rate were determined by different release apparatus and USP dissolution apparatus and were found to be independent of pH of environment and stirring conditions. In vitro release rate were similar to in vitro studies conducted on dogs.

Kendall et al(1982) (Barclay,1992) conducted a cross over double blind study on conventional sustained release formulation and osmotic pump system was found to be consistent with its in vitro release profile , in that the formulation produced constant plasma level over longer period compared with the slow release formulation. Osmotic pump formulation elicited a more uniform hemodynamic response and greater pre dosing effect when administered once daily.

Bayne et al (1982) (Haslam et al, 1989) evaluated two osmotic ally driven controlled release dosage form of Indomethacin in a multiple dose crossover study in 12 healthy subjects. Following equivalent daily doses ,less frequent dosing of both controlled release form result in plasma concentration profile that were more uniform than those following capsule regime.

Liu and coworker (Liu et al, 1984) conducted in vitro studies to compare the release of phenyl Propranololamine hychloride from oral osmotic pump and one marketed long acting appetite suppressant product (spansules) .It was found that osmotic pressure on the delivery rate was observed at a pH 1.2 or 7.4 , The effect of environmental osmotic pressure on the delivery rate was observed with increase in the O.P. Controlled DDS system provide better control over drug release than the sustained release Spansule system.

Bindschaedler et al (1986) (Banker et al,1995) reported their study on EOP of KCl with cellular acetate coating prepared from organic solution or aqueous dispersion .A release orifice of 250μm was created using a micro drill and release experiment were conducted in 500ml distill water .Based on their observation the author concluded that aqueous based latex film exhibit a shorter log time to constant release with higher release rate in comparison to organic based coating of the same film weight.

Ramadan and Towashi (1987) (Towashi et al,1987) investigated the effect of hydrodynamic condition and orifice Seize on drug release rate from EOP system. In this study neat KCl tablet were prepared ,coated in occuralence with patent literature and orifice of various seize were mechanically created .Release characteristic were examine using the USP basket method at different rotation found to be dependent on rotational speed of particular apparatus .However the release rate was considerably higher under turbulent condition operating in Tubular mixture. Using USP rotating basket at low stirring rate and at static condition the drug release rate deviate from zero order. The author explain that increase in drug delivery as a function of fluid velocity could be due to agitation increase water influx into the core of the EOP by forcing water through the pores of the membrane and /or through the delivery orifice.

In another study EOP of salbutamol (Godbillion et al, 1985) were developed and the different variables affecting the drug release studies. Release rate decreases with increasing coat thickness but were not affected by the compression forces or porosity .Drug release was also affected by the osmotic agent concentration.

Swanson et al (1987) (Swanson et al, 1987) detail the development of push pull osmotic pump for 24hr oral controlled delivery of the Nifedipine. Zero order drug release rate for the system was 1.7, 3.4, and 5.1 mg/hr and the total amount of drug release was 30, 60 and 90mg respectively.

Classification (Mishra et al, 2006)

The OCODDS can be conveniently classified in to following types:

- **Single chamber osmotic pump**
  1. Elementary osmotic pump
- **Multi chamber osmotic pump**
  1. Push pull osmotic pump.
  2. Osmotic pump with non expanding second chamber.
- **Specific types**
  1. Controlled porosity osmotic pump.
  2. Monolithic osmotic systems.
  3. Osmotic bursting osmotic pump.
  4. OROS – CT
  5. Multi particulate delayed release systems (MPDRS)
  6. Liquid Oral Osmotic System.(L-OROS)

❖ **Single chamber osmotic pump**

1. **Elementary osmotic pump (EOP):**

It works on the same mechanism as the impala table pumps it is simplest possible form of osmotic pump as it does not require special equipment and technology .This device was further simplification of Higuchi – Theeuwes pump. It was developed in the year 1975 by Theeuwes (Santus et al,1995) The EOP consist of single layered tablet core containing a water soluble drug with or without other osmotic agent .A semi permeable membrane surrounds the tablet core. When such a system is swallowed water from the GIT enter through the membrane in the core, the drug dissolved and the drug solution is pumped out through the exit orifice. This process continues at a constant rate until the entire solid drug inside the tablet has been dissolved drug continues to be delivered but at a declining rate until the osmotic pressure between outside environment and saturated drug solution .Normally the EOP delivers 60 - 80% of its content at a constant rate and there is a short lag time of 30- 60 min as the system hydrates before zero order drug release from the EOP is obtained.

Factors affecting the release rate from EOP

There are following factors which should be considered while designing an EOP. These factors are also applicable to other osmotic drug delivery systems:

1. Membrane thickness.
2. Osmotic pressure.
3. Type of membrane and characteristics.
4. Solubility.
5. Seize of the delivery orifice.
6. Use of Wicking agent.
7. Type and amount of plasticizer.

1. **Membrane thickness**: - A principle factor controlling the rate of penetration of water into the dispenser is the thickness of the membrane. The permeability of water into the membrane can be enhanced by the choice of a suitable type of the membrane material. The time of release of the active constituent can be easily varied by as much as 1000 fold based upon the thickness of the membrane. In general the rate of drug release can be achieved by varying the membrane material, while small change up to a five percent can be best achieve by varying the thickness of the membrane.

2. **Osmotic pressure**:- From the equation :-

$$F(z) = 1\text{-}s/p \text{ ---------- (11)}$$

Where

S = Solubility of drug.

F(z) = Release of drug in zero order kinetics.

P = Density of core tablet.

So from the equation it is clear that the rate of drug release from an osmotic system is directly proportional to the osmotic pressure of the core formulation If a semipermiable membrane separates a solution from the pure water or two solution of different drug concentration the tendency to equalize concentration will result in the inflow of water from the less drug concentration solution to the other end .So it is important to optimized the osmotic pressure gradient between the inside compartment and to the external environment.

The osmotic pressure can also be found out by the Van't Hoff equation:-

$$\pi = CRT \text{ ---------- (12)}$$

Where:

π = Osmotic pressure of the solution.

C = Molar concentration of the solute in the solution.

R = Gas constant.

T = Absolute temperature.

A few trial calculation has shown that the osmotic pressure of the saturated solution of even moderately soluble compound are very highly and of even moderately soluble compound are very high and of the order of several hundreds and even thousands of pound per square inch pressure.

If desirable osmotic pressure is not obtained then a second compound is incorporated called as an osmotic attractant agent [5]with the active agent into enclosure. The osmotic attractant is drawn from those compounds such as:

a. Having high osmotic pressure.

b. Do not degrade.

c. Don't interfere with the membrane or enclosed wall.

d. Do not interfere with action of the active drug molecule or the environment into which it is ultimately released.

e. Do not degrade very quickly.

Table No 2: Some of the commercially (Santus et al, 1995; Mishra et al, 2006) used osmotic agents along with their osmotic pressure

Compound / Mixture	Osmotic pressure (atm)
Sodium chloride	356
Fructose	355
Potassium chloride	245
Sucrose	150
Xylitol	104
Sorbitol	84
Dextrose	82
Citric acid	69
Tartaric acid	67
Mannitol	38
Potassium sulphate	39
Lactose	23
Fumaric acid	10
Adipic acid	8

Potassium phosphate.	105
Melanic acid	117
Lactose – Fructose	500
Dextrose – Fructose	450
Sucrose – Fructose	430
Mannitol – Fructose	415
Lactose - sucrose	250
Lactose – Dextrose	225
Mannitol – Dextrose	225
Dextrose – Sucrose	190
Mannitol - Sucrose	170
Mannitol - Lactose	130
Sodium phosphate Tribasic $12H_2O$	36
Sodium phosphate dibasic 7 H_2O	31
Sodium phosphate dibasic $12H_2O$	31
Sodium phosphate Dibasic anhydride	29
Sodium phosphate Monobasic .H_2O	28

3. Type of membrane and characteristics: Drug release from an osmotic system is largely independent of the pH and agitation intensity of GIT tract(Wilson CG ,2000). This is because of its selective water permeable membrane and effective isolation of dissolution process of drug core from the gut environment. The in – vivo release rate of the system is therefore independent of its position in the GIT, because the membrane in the osmotic system is semi permeable in nature any polymer that is permeable to water but impermeable to solute (drug, organic and inorganic ions) can be selected example include cellulose ester such as cellulose acetate, cellulose diacetate, cellulose triacetate, cellulose propionate, and cellulose ether such as ethyl cellulose and Eudragit (Bhatt, 2004). Among the cellulose polymer cellulose acetate membrane are mostly used because of its high water permeability characteristics and it can be adjusted varying the degree of acetylation of the polymer. The permeability of this membrane can be increased further by adding plasticizer to the polymer, which increases the water diffusion coefficient or hydrophilic flux enhancer which increases the water sorption of the membrane. A few example of hydrophilic flux enhancer are Polyethylene glycols 300, 400, 600, 1500, 4000, and 6000(Ramakrishna, 2001)

Ideal Property of Semi Permeable Membrane

The Semi Permeable Membrane must meet some performance criteria

1. The material must posses sufficient wet strength (-10^5) and wet modulus so as to retain its dimensional integrity during the operational lifetime of the device.

2. The membrane exhibit sufficient water permeability so as to retain water flux rate in the desired range. The water vapor transmission rates can be used to estimate water flux rates

3. The reflection coefficient and leakiness of the osmotic agent should approach the limiting value of unity. Unfortunately, polymer membranes that are more permeable to water are also, in general more permeable to the osmotic agent.

4. The membrane should also be biocompatible.

4. Solubility: In the case of the EOP solubility is one of the most important factor affecting the drug release kinetics from the osmotic pumps. Assuming the tablet core of pure drug, the fraction of core drug release with zero order kinetics is given by the equation no (11). The drug with the solubility of ≤ 0.05 g/cm^2 would release the drug $\geq 95\%$ by the zero order kinetics according the equation (11). On other hand Zero order release rate would be slow according to the equation (7) because of the small osmotic pressure and drug solubility .At the same time highly water soluble drugs (≥ 0.3 g/cm^3) would be zero order for small percentage of the initial drug load .Thus the intrinsic water solubility of many drug might preclude them from incorporation in an osmotic pump of EOP design. Candidate drug for osmotic delivery should have solubility within the range of 50- 300 mg/ml.

5. Size of the delivery orifice: The orifice is one of the most important parts in the membrane for the drug release. The size of the orifice must be optimized in order to control the drug release from the osmotic system. In the case of a formulation delivery orifice the size must be smaller than the maximum seize (A_{max}) to minimized the solute diffusion through the orifice .The hydrostatic pressure may not be relived because small seize of orifice may lead to deformation of the delivery system there resulting in unpredictable drug release.

6. **Use of Wicking agent** : The wicking agent are those agents which help to increase the contact surface area of the drug with the incoming aqueous fluid. The use of the wicking agent help to enhance the rate of drug released from the orifice of the drug. The examples are colloidal silicon dioxide, PVP & Sodium laryl sulphate.

7. **Type and amount of plasticizer:** In a pharmaceutical industry coatings, plasticizers & low molecular weight diluents are added to modify the physical properties and improves film forming characteristic of polymers. The plasticizers can turn a hard and brittle polymer into a softer, more pliable material & make it more resistant to mechanical stress. The polymer can affect the permeability of the polymer films can result in the rate of change of drug release from the osmotic tablets.

❖ **Multi chamber osmotic pump**

Push pull osmotic pump

Push pull osmotic pump is a modified EOP (Vyas et al, 2001; Barclay et al, 1987) 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.

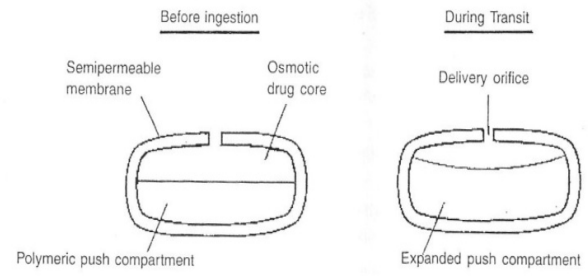

Figure 6 The commercially using push pull systems include **Glucotrol XL**, **Procardia XL**, **Concerta.**

Osmotic Pump with Non Expanding Second Chamber

The second category of multi-chamber devices comprises system containing a non-expanding second chamber (Srenivasa et al, 2001). 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. Example: The problem that leads to withdrawal of osmosin, the device consists of a normal drug containing porous tablet from which drug is released as a saturated solution. However before the drug can escape from the device it must pass through a second chamber. Water is also drawn osmotically into this chamber either because of osmotic pressure of drug solution or because the second chamber contain, water soluble diluents such as NaCl. This type of devices consist of two rigid chamber, the first chamber contains a biologically inert osmotic agent, such as sugar or a simple salt like sodium chloride, the second chamber contains the drug. In use water is drawn into both the chamber through the surrounding semi permeable membrane. The solution of osmotic agent formed in the first chamber then passes through the connecting hole to the drug chamber where it mixes with the drug solution before exiting through the micro porous membrane that form a part of wall surrounding the chamber. The device could be used to deliver relatively insoluble drugs.

Specific types

Control porosity osmotic pump (CPOP) : CPOP is an attempt to circumvent the need for a laser or mechanical drilled orifice. In CPOP the orifice through which drug is released are formed by incorporation of a leachable water soluble component in the coating material. (Mishra et al, 2006)

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

The CPOP has an advantage as drug is released from the whole surface of device rather than from the single hole which may reduce stomach irritation problem hole is formed by a coating procedure hence complicated laser drilling is not required and the tablet can be made as very small by using drug pills coated by appropriate membrane.

Monolithic osmotic systems.

It constitutes a simple dispersion of water-soluble agent in polymer matrix. When the system comes in contact in with the aqueous environment water imbibitions by the active agents takes place rupturing the polymer matrix capsule surrounding the drug, thus liberating it to the outside environment (Mishra et al, 2006). Initially this process occurs at 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 liter of the active agents is incorporated in to the device as above this level, significant contribution from the simple leaching of the substance take place.

Osmotic bursting osmotic pump

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 (Vyas et al, 2001). 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

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 (Vyas et al, 2001) .After coming in contact with the GIT fluid gelatin capsule dissolve 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.

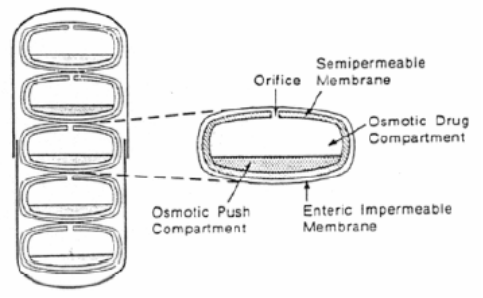

Figure no 7

Multi particulate delayed release systems (MPDRS)

MPDRS consist of pellets comprises of drug with or without osmotic agent, which are coated with a semipermiable membrane .When this system comes in contact with the aqueous environment, water penetrates in the core and forms a saturated solution of soluble component(Schultzew et al,1997). The osmotic pressure difference results in rapid expansion of the membrane, leading to the formation of pores. The osmotic agent and the drug released through the pores according to zero order kinetics. The lag time and dissolution rate were found to be dependent on the coating level and the osmotic properties of the dissolution medium.

Liquid Oral Osmotic System (L-OROS)

To overcome the drug solubility issue Alza developed the L-OROS system where the liquid soft gelatin product containing the drug in a dissolved state is initially manufactured and then cated with a barrier membrane, then the osmotic push layer and then semi permeable membrane containing a drilled orifice(Garg et al, 2002). Liquid OROS are designed to deliver drugs as liquid formulations and combine the benefits of extended release with high bioavailability (Dong et al, 2000). They are of three types: -

1. L- OROS hard cap,

2. L- OROS soft cap

3. 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 (Theeuwees et al, 1983). Where as L OROS hard cap or soft cap 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. (Haslam et al, 1989)

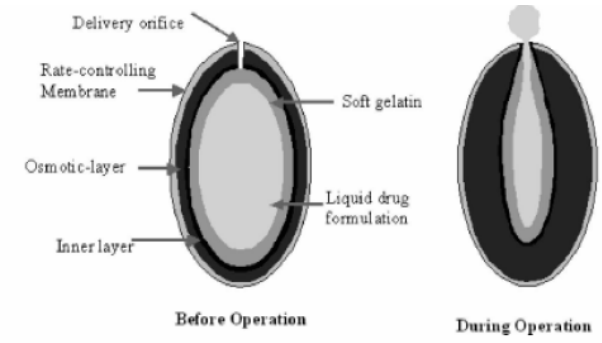

Figure no 8

❖ **Recent trends**

1. Sandwiched osmotic tablet (SOT)

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 agents' 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 (Liu et al, 2000)

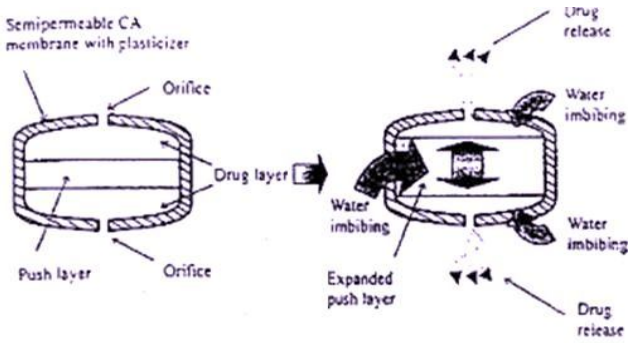

Figure No 9

2. 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 (Chein et al, 1984) The bilayer capsule 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 slidable 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 (Santus et al,1995)

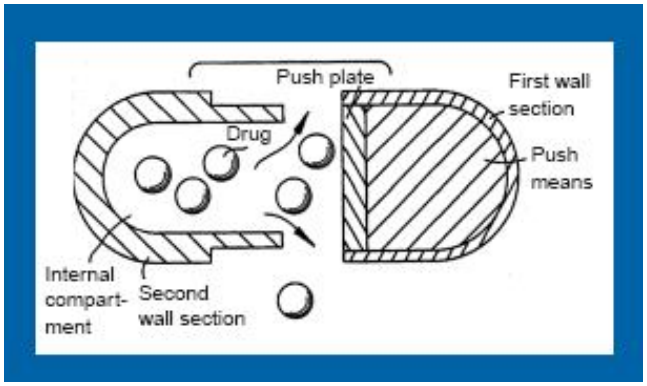

Fig (10):- Telescopic capsule

Pulsatile delivery based on expandable orifice

Patent 5318558 (1994) and 5221278 (1993) assigned to Alza claim the pulsatile delivery of agent from osmotic systems based on the technology of an expandable orifice (Mishra et al,2000) The system is in the form of capsule from which the drug is delivered by the capsule's osmotic infusion of moisture from the body. The delivery orifice opens intermittently to achieve a pulsatile delivery effect. The orifice formed in the capsule wall, which is constructed of an elastic material. As the osmotic infusion progresses, pressure rises with in the capsule causing the wall to stretch (Ramdan et al,1987). The orifice is small enough so that when the elastic wall relaxes, the flow of the drug through the orifice essentially stops, but when the elastic wall stretches beyond the threshold because of increase of pressure, the orifice expands sufficiently to allow the drug to be release at a required rate. Elastomers such as Styrene- Butadiene copolymer can be used.

Pulsatile delivery by a series of stops

Patent 5209746 also assigned to Alza described an implantable capsule for pulsatile delivery (Santus et al,1995). The capsule consists of drug and absorptive osmotic agent engine that are each placed in the compartments separated by a movable partition. Pulsatile delivery is achieved by a series of stop along the inner wall of the capsule. These stop obstruct the movement of the partition but overcome in succession as the osmotic pressure rises above the threshold level. The no of stops and the longitudinal placement of the stops along the length of the capsule dictate the no and frequency of pulses and the configuration of the partition controls the pulse intensity. Reports document that Porcine somatotropine has been delivered by this system.

Miscellaneous devices:

Patent 6352721 (2002) assigned to Osmotica Corporation (Tortola, British Virgin Islands) report a combined diffusion osmotic pump drug delivery system . The device has a centrally located expandable core that is completely surrounded by active substances- containing layer, which is completely surrounded by a membrane. The core consist of an expandable hydrophilic polymer and an optional osmogen (Kaushal et al, 2003).The composition is completely surrounding the core comprises an active substances, an osmogent and an osmopolymer. The membrane is microporous in nature and may have a delivery orifice. The device is capable of delivering insoluble, slightly soluble, sparingly soluble and very soluble drug to the environment.

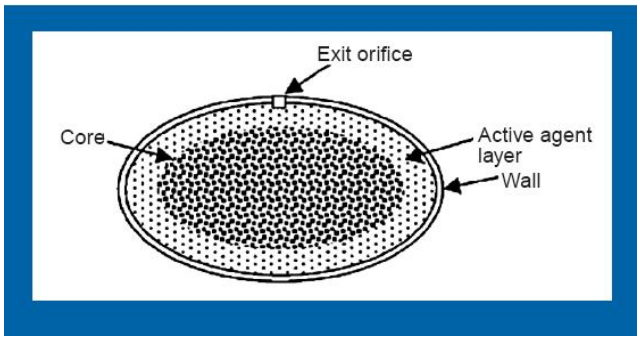

Fig no 11: Miscellaneous device

Lipid osmotic pump

Merk describes an osmotic pump for the lipid delivery as shown in the figure. The device concerns an osmotic agent for dispensing benificial active agent that has poor solubility in water. The core of the system comprises a beneficial amount of a sustantially water- insoluble active agent, which is lipid soluble or lipid- wettable; a sufficient amount of water insoluble lipid carrier, which is liquid at the temperature of use to dissolve or suspend the drug and agent to ensure the release of the lipid carrier of the drug from the pump (Godbillion et al, 1985) The water insoluble wall is microporous and is wetted by lipid carrier. The device is prepared by first dissolving the drug of interest in the lipid vehicle. The osmogent (Sodium chloride) is dispersed in the melted lipid and

then quenched-cool to form form a lump that are broken and made into tablet. The microporous is coated at a moderate flow of unheated ambient air.

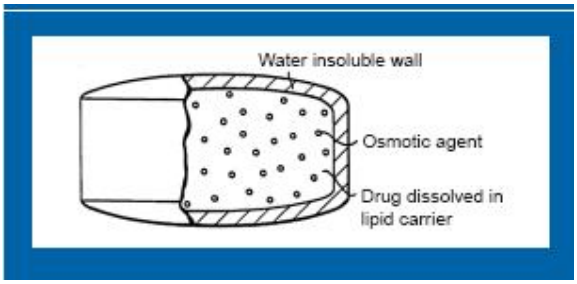

Figure no 12

Patents on Osmotic drug delivery system

The patent on osmotic drug delivery system is given on the Table no 3 and Table no 4.

Table : 3 Patents of drug formulation in the form of Elementary Osmotic pump (Barclay et al, 1987)

Year	U.S.Patent No.	Drug
1981	4265874	Indomethacin
1981	4305927	Acetazolamide
1984	4439195	Theophylline
1984	4484921	Theophtylline
1986	4610686	Haloperidol
1987	4662880	Pseudoephedrine & Bromopheniramine
1988	4732915	Haloperidol
1988	4751071	Salbutamol
1989	4857330	Chlorpheniramine
1991	4986987	Imenhydrinate
1992	147654	Buccal nicotine
1993	200194	Mucosal delivery of anti-plague agent and nicotine.
1998	5776493	Mucosal delivery of Nystatin
1999	5869096	Mucosal osmotic delivery of Levodopa.
2003	20030143272	Nifedipine formulation
2005	20050053653	Low water soluble drugs

CONCLUSION

The OCODDOS has travelled a long way right from the time discovery, it gone through various types of upliftment. The osmotic drug development is slightly costly type of drug delivery system but it tends to provide a good rate of drug release which tends to increase its acceptance in the pharmaceutical world.

Table 4 Patent of drug formulation in the form of Multi chamber osmotic pump

Year	US Patent	Drug
1986	4612008	Diclofenac sodium
1988	4765989	Nifedipine and α blocker
1988	4783337	Calcium antagonist, ACE inhibitor
1989	4812263	Isadipine
1989	4837111	Doxazocin
1989	4859470	Diltiazem
1990	4904474	Beclomethasone
1990	4948593	Contraceptive Steroid
1991	5024843	Glpizide
1991	5028434	Nivadipine
1992	5160744	Verapamil
1992	5091190	Glipizide
1993	5185158	Tandospirone
1993	5192550	Antiparkinsons drug
1993	5248310	Beclomethasone(oral)
1996	5545413	Glipizide
1997	5591454	Glipizide
2003	20030224051	Oxycodone
2004	20040091529	Topiramine
2005	20050232995	Resperidone and Paliperidone

Table No: 5 Patent of drugs formulated in the form of other osmotic delivery system

Year	US Patent Number	Drugs
1976	3952741	Vitamine and hormones
1984	4428926	Propanolol
1984	4432965	Qunidine
1987	4687660	Burinorphine
1988	4769027	Psuedoepidrine HCl
1989	4851228	Indomethacine trihydride
1989	4880631	Diltizem HCl
1990	4968507	Diltiazem
1990	4975284	Potassium Chloride
1993	5209746	Porcine Somatotropine
2005	20050010196	Leuprolid

Table : 6 Examples of some marketed band of **Osmotic drug delivery system**

Product name	Chemical name	Type of delivery	Developer/ Marketer
Acutrim	Phenylpropanolamine	Elementary pump	Alza/Heritage
Alpress LP	Prazosin	Push -Pull	Alza/Pfizer
Cardura XL	Doxazosin	Push -Pull	Alza/Pfizer
CalanSR	Verapamil		Alza/GD Searle &Co
Concerta	Methyl phenidate		Alza
Covera HS	Verapamil	Push -Pull with time delay	Alza/GD searle
Ditropan XL	Oxybutinin chloride	Push -Pull	Alza/UCB Pharma
Dynacirc CR	Isradipine	Push -Pull	Aza/Novartis
Efidac 24	Pseudoephiderine	Elementary Pump	Aza/Novartis
Efidac 24	Chlorpheniramine meleate	Elementary Pump	Aza/Novartis
Glucotrol XL	Glipizide	Push - Pull	Alza/Pfizer
MinipressXL	Prazosine	Push-Pull	Alza/Pfizer
ProcadiaXL	Nifedipine	Push-Pull	Alza/Pfizer
Sudafed 24hours	Pseudoephidrine	Push-Pull	Alza/Warner Lambert
Teczam	Enapril and Diltiazem	Elementary Pump	Merck/Aventis
Tiamate	Diltiazem	Push-Pull	Merck/Aventis
Volmax	Albuterol	Push-Pull	Alza/Muro Pharmaceuticals

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