Prudvi Kanth N. *et al.* / *International Journal of Pharmacy & Therapeutics*, 4(3), 2013, 200-211.

e- ISSN 0976-0342
Print ISSN 2229-7456

International Journal of Pharmacy & Therapeutics

Journal homepage: www.ijptjournal.com

IJPT

OSMOTIC DRUG DELIVERY SYSTEM-RECENT UPDATES

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ABSTRACT

Conventional drug delivery systems have little control over their drug release and almost no control over the effective concentration at the target site. This kind of dosing pattern may result in constantly changing, unpredictable plasma concentrations. Drugs can be delivered in a controlled pattern over a long period of time by the process of osmosis. Osmotic devices are the most promising strategy based systems for controlled drug delivery. They are the most reliable controlled drug delivery systems and could be employed as oral drug delivery systems. The present review is concerned with the study of drug release systems which are tablets coated with walls of controlled porosity. When these systems are exposed to water, low levels of water soluble additive is leached from polymeric material i.e. semi permeable membrane and drug releases in a controlled manner over an extended period of time. Drug delivery from this system is not influenced by the different physiological factors within the gut lumen and the release characteristics can be predicted easily from the known properties of the drug and the dosage form. In this paper, various types of osmotically controlled drug delivery systems and the basic components of controlled porosity osmotic pump tablets have been discussed briefly. In osmotic delivery systems, osmotic pressure provides the driving force for drug release. Increasing pressure inside the dosage form from water incursion causes the drug to release from the system.

Key Words:- Osmosis, Osmotic pressure, Osmogen, Semi permeable membrane, Osmotic pumps.

INTRODUCTION

Many conventional drug delivery systems have been designed by various researchers to modulate the release a drug over an extended period of time and release (Arora S *et al.,* 2006; Rajesh AK *et al.,* 2011; Simon H *et al.,* 2012). The rate and extent of drug absorption from conventional formulations may vary greatly depending on the factors such as physico-chemical properties of the drug, presence of excipients, physiological factors such as presence or absence of food, pH of the gastro-intestinal tract (GI) (Bhatt PP *et al.,* 2004). However, drug release from oral controlled release dosage forms may be affected by pH, GI motility and presence of food in the GI tract (Banker RW *et al.,* 1987). Drugs can be delivered in a controlled pattern over a long period of time by the process of osmosis. Drug delivery from this system is not influenced by the different physiological factors within the gut lumen and the release characteristics can be pre-dicted easily from the known properties of the drug and the dosage form (Conley R *et al.,* 2006). Osmotically controlled drug delivery system, deliver the drug in a large extent and the delivery nature is independent of the physiological factors of the gastrointestinal tract and these systems can be utilized for systemic as well as targeted delivery of drugs. Osmotically controlled oral drug delivery systems utilize osmotic pressure for controlled delivery of active agents (Chein YW *et al.,* 2005).

Among the controlled release devices, osmotically controlled hold a stable place because of its

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reliability to deliver the API at predetermined zero order rate for prolonged period of time so these are used as the standard dosage forms for the constant delivery of contents. Osmotic Pump Controlled Release Preparation is a novel drug delivery system with eternally drug delivery rate as characteristic and controlled with the osmotic pressure difference between inside and outside of the semipermeable membrane as drug delivery power (Cortese R *et al.,* 1982).

Recently, osmotic tablets have been developed in which the delivery orifice is formed by the incorporation of a leachable component in the coating. Once the tablet comes in contact with the aqueous environment, the water-soluble component dissolves, and an osmotic pumping system results. Subsequently, water diffuses into the core through gradient and thereby controlling the release of drug (Dwarakanadha Reddy P *et al.,* 2010).

Osmosis

Osmosis can be defined as the spontaneous movement of a solvent from a solution of lower solute concentration to a solution of higher solute concentration through an ideal semi permeable membrane, which is permeable only to the solvent but impermeable to the solute. The pressure applied to the higher-concentration side to inhibit solvent flow is called the osmotic pressure.

Osmotic pressure

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

$\pi = n2\ RT$ (eq…1)

Where, π = osmotic coefficient
n2 = molar concentration of solute in the solution
R = gas constant
T = Absolute temperature

Osmotic pressure is a colligative property, which depends on concentration of solute that contributes to osmotic pressure. Solutions of different concentrations having the same solute and solvent system exhibit an osmotic pressure proportional to their concentrations. Thus a constant osmotic pressure, and thereby a constant influx of water can be achieved by an osmotic delivery system that the microporous membrane, setting up an osmotic results in a constant zero order release rate of drug (Eckenhoff B *et al.,* 1987). The rate of drug release from osmotic pump depends on the drug solubility and the osmotic pressure of the core; hence, these systems are suitable for delivery of drugs with moderate water solubility.

General Mechanism for Drug Release from Osmotic Pumps

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

$dM/dt = dV/dt \times c$ (eq…2)

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

But, $dV/dt = (A/h)\ Lp\ (\sigma \Delta\pi - \Delta p)$ (eq**…3)**
Where, A = membrane area,
h = thickness of membrane,
Lp= mechanical permeability,
σ = reflection coefficient,
$\Delta\pi$ = osmotic pressure difference,
Δp = hydrostatic pressure difference.
As the size of orifice delivery increases, Δp decrease, so $\Delta\pi >> \Delta p$ and equation becomes

$dV/dt = A/h\ Lp\ (\sigma \Delta\pi)$ (eq…4)

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

$dV/dt = A/h\ Lp\ \sigma\pi = A/hk\ \pi$ (eq…5)
($k = Lp\sigma$ = membrane permeability)
Now, equation (2) can be given as

$dM/dt = (A/h)\ k\ \pi\ c = (A/h)\ k\ \pi\ S$ (eq…6)
(S = solubility of drug, c taken as S)

Advantages of Osmotic Drug Delivery Systems

Osmotic drug delivery systems for oral and parenterals use offer distinct and practical advantages over other means of delivery. The following advantages have contributed to the popularity of osmotic drug delivery systems (Higuchi T *et al.,* 1973; Leeper HM *et al.,* 1976).

1. The delivery rate of zero-order is achievable with osmotic systems.
2. Delivery may be delayed or pulsed, if desired.
3. Higher release rates are possible with osmotic systems compared with conventional diffusion-controlled drug delivery systems.

4. The release rate of osmotic systems is highly predictable and can be programmed by modulating the release control parameters.
5. For oral osmotic systems, drug release is independent of gastric pH and hydrodynamic conditions.
6. The release from osmotic systems is minimally affected by the presence of food in gastrointestinal tract.
7. A high degree of in vivo- in vitro correlation (IVIVC) is obtained in osmotic systems.

Limitations of Osmotic Drug Delivery Systems

1. Special equipment is required for making an orifice in the system.
2. Residence time of the system in the body varies with the gastric motility and food intake.
3. It may cause irritation or ulcer due to release of saturated solution of drug (Haslem J *et al.,* 1989; Herbig SM *et al.,* 1995)

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Key Parameters that Influence the Design of Osmotic Controlled Drug Delivery Systems

Orifice size

To achieve an optimal zero-order delivery profile, the cross-sectional area of the orifice must be smaller than a maximum size to minimize drug delivery by diffusion through the orifice. Furthermore, the area must be sufficiently large, above a minimum size to minimize hydrostatic pressure buildup in the system. Otherwise, the hydrostatic pressure can deform 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 (Higuchi T *et al.,* 1973; Jensen JL *et al.,* 1995).

Methods to create a delivery orifice in the osmotic tablet coating are:

- Mechanical drill
- Laser drill: This technology is well established for producing sub-millimeter size hole in tablets. Normally, CO2 laser beam (with output wavelength of 10.6μ) is used for drilling purpose, which offers excellent reliability characteristics at low costs (Jerzewski R *et al.,* 1992; Kaushal AM *et al.,* 2003).
- Indentation that is not covered during the coating process: Indentation is made in core tablets by using modified punches having needle on upper punch. This indentation is not covered during coating process which acts as a path for drug release in osmotic system.
- Use of leachable substances in the semi permeable coating e.g. controlled porosity osmotic pump

Solubility

The release rate depends on the solubility of the solute inside the drug delivery system. Therefore, drugs should have sufficient solubility to be delivered by osmotic delivery. In the case of low solubility compounds, several alternate strategies may be employed. Broadly, the approaches can be divided into two categories. First, swellable polymers can be added that result in the delivery of poorly soluble drugs in the form of a suspension. Second, the drug solubility can be modified employing different methods such as co compression of the drug with other excipients which improve the solubility. For example, cyclodextrin can be included in the formulation to enhance drug solubility. Additionally, alternative salt forms of the drug can be employed to modulate solubility to a reasonable level. In one case, the solubility of oxprenolol is decreased by preparing its succinate salt so that a reduced saturation concentration is maintained (Khanna SC *et al.,* 1997; Jasti BR *et al.,* 2006).

Osmotic pressure

The osmotic pressure π directly affects the release rate. To achieve a zero-order release rate, it is essential to keep π constant by maintaining a saturated solute solution. Many times, the osmotic pressure generated by the saturated drug solution may not be sufficient to achieve the required driving force. In this case, other osmotic agents are added that enhance osmotic pressure. For example, addition of bicarbonate salt not only provides the necessary osmotic gradient but also prevents clogging of the orifice by precipitated drug by producing an effervescent action in acidic media (Mishra B *et al.,* 2006; McClelland GA *et al.,* 1991).

Semi permeable membrane

Since the semi permeable membrane is permeable to water and not to ions, the release rate is essentially independent of the pH of the environment. Additionally, the drug dissolution process takes place inside the delivery system, completely separated from the environment (Madhavi B *et al.,* 2006).

Basic Components of Osmotic Systems

Drug

Which have short biological half-life and which is used for prolonged treatment are ideal candidate for osmotic systems. Various drug candidates such as Diltiazem HCl, Carbamazepine, Metoprolol, Oxprenolol, Nifedipine, Glipizide etc are formulated as osmotic delivery **(**Makhija Sapna N *et al.,* 2003; Malaterre V *et al.*)

Semipermeable membrane

An important part of the osmotic drug delivery system is the semipermeable membrane housing. Therefore, the polymeric membrane selection is key to the osmotic delivery formulation. The membrane should possess certain characteristics, such as impermeability to the passage of drug and other ingredients present in the compartments. The membrane should be inert and maintain its dimensional integrity to provide a constant osmotic driving force during drug delivery. Any polymer that is permeable to water but impermeable to solute can be used as a coating material in osmotic devices. e.g. Cellulose esters like cellulose acetate, cellulose acetate butyrate, cellulose triacetate and ethyl cellulose and Eudragits.

Osmotic agent

Osmotic agents maintain a concentration gradient across the membrane. They also generate a driving force for the uptake of water and assist in maintaining drug uniformity in the hydrated formulation. Osmotic components usually are ionic compounds consisting of either inorganic salts or hydrophilic polymers. Osmotic agents can be any salt such as sodium chloride, potassium chloride, or sulfates of sodium or potassium and lithium. Additionally, sugars such as glucose, sorbitol, or sucrose or inorganic salts of carbohydrates can act as osmotic agents. The polymers may be formulated along with poly(cellulose), osmotic solutes, or colorants such as ferric oxide. Swellable polymers such as poly(alkylene oxide), poly(ethylene oxide), and poly (alkalicarboxymethylcellulose) are also included in the push layer of certain osmotic systems. Further, hydrogels such as Carbopol (acidic carboxypolymer), Cyanamer (polyacrylamides), and Aqua-Keeps (acrylate polymer polysaccharides composed of condensed glucose units such as diester cross-linked polygluran) may be used.

Flux regulators

Delivery systems can be designed to regulate the permeability of the fluid by incorporating fluxregulating agents in the layer. Hydrophilic substances such as polyethethylene glycols (300 to 6000 Da), polyhydric alcohols, polyalkylene glycols, and the like improve the flux, whereas hydrophobic materials such as phthalates substituted with an alkyl or alkoxy (e.g., diethyl phthalate or dimethoxy ethylphthalate) tend to decrease the flux. Insoluble salts or insoluble oxides, which are substantially water-impermeable materials, also can be used for this purpose .

Wicking agent

A wicking agent is defined as a material with the ability to draw water into the porous network of a delivery device. A wicking agent is of either swellable or non-swellable nature. They are characterized by having the ability to undergo physisorption with water. Physisorption is a form of absorption in which the solvent molecules can loosely adhere to surfaces of the wicking agent via Vander Waals interactions between the surface of the wicking agent and the adsorbed molecule. The function of the wicking agent is to carry water to surfaces inside the core of the tablet, thereby creating channels or a network of increased surface area. Materials, which suitably for act as wicking agents include colloidal silicon dioxide, aolin, titanium dioxide, alumina, niacinamide, sodium lauryl sulphate (SLS), low molecular weight poly vinyl pyrrolidone (PVP), m-pyrol, bentonite, magnesium aluminium silicate, polyester and polyethylene.

Pore forming agent

These agents are particularly used in the pumps developed for poorly water soluble drug and in the development of controlled porosity or multiparticulate osmotic pumps. These poreforming agents cause the formation of microporous membrane. The microporous wall may be formed in situ by a pore-former by its leaching during the operation of the system. The pore formers can be inorganic or organic and solid or liquid in nature.For example, alkaline metal salts such as sodium chloride, sodium bromide, potassium chloride, potassium sulphate, potassium phosphate etc., alkaline earth metals such as calcium chloride and calcium nitrate, carbohydrates such as sucrose, glucose, fructose, mannose, lactose, sorbitol, mannitol and, diols and polyols such as poly hyric alcohols and polyvinyl pyrrolidone can be used as pore forming agents.

Coating solvent

Solvents suitable for making polymeric solution that is used for manufacturing the wall of the osmotic device include inert inorganic and organic solvents that do not adversely harm the core, wall and other materials. The typical solvents include methylene chloride, acetone, methanol, ethanol, isopropyl alcohal, butyl alcohal, ethyl acetate, cyclohexane, carbon tetrachloride, water etc. 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) etc. can be used.

Plasticizers

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

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

Types of Osmotic Pumps

Based on their design and the state of active ingredient, osmotic delivery systems can be classified as follows (Malaterre V *et al*.; Rajesh A. Keraliya *et al*., 2011; Simon Herrlich *et al*., 2012; Zentner GM *et al*., 1985):

Osmotic delivery systems for solids

Type I

Single compartment: In this design, the drug and the osmotic agent are located in the same compartment and are surrounded by the semipermeable membrane (SPM). Both the core components are dissolved by water, which enters the core via osmosis. A limitation is the dilution of drug solution with the osmotic solution, which affects the release rate of the drug from the system. Additionally, water-incompatible or water-insoluble drugs cannot be delivered effectively from a single compartment configuration.

Type II

Multiple compartments: In this design, drug is separated from the osmotic compartment by an optional flexible film, which is displaced by the increased pressure in the surrounding osmotic compartment, which, in turn, displaces the drug solution or suspension. The type II system inherently has greater utility than type I systems and can deliver drugs at a desired rate independent of their solubilities in water. One main advantage of these systems is their ability to deliver drugs that are incompatible with commonly used electrolytes or osmotic agents.

Osmotic delivery systems for liquids

Active ingredients in liquid form are difficult to deliver from controlled release platforms because they tend to leak in their native form. Therefore, liquid active agents typically are enclosed in a soft gelatin capsule, which is surrounded by an osmotic layer that, in turn, is coated with a semipermeable membrane. When the system takes up water from its surroundings, the osmotic layer squeezes the innermost drug reservoir. The increasing internal pressure displaces the liquid from the system via a rupturing soft gelatin capsule.

Historical aspects of osmotic pumps

About 75 years after discovery of the osmosis principle, it was first used in the design of drug delivery systems. Rose and Nelson, the Australian scientists, were initiators of osmotic drug delivery. In 1955, they developed an implantable pump, which consisted of three chambers: a drug chamber, a salt chamber contains excess solid salt, and a water chamber. The drug and water chambers are separated by rigid semi permeable 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.

Several simplifications in Rose-Nelson pump were made by Alza Corporation in early 1970s. The kinetics of pumping from Rose Nelson pump is given by the following equation:

$$\frac{dMt}{dt} = \left(\frac{dV}{dt}\right) \cdot C,$$

where *dMt/dt* is the drug release rate, *dV/dt* is the volume flow of water into the salt chamber, and *C* represents the concentration of drug in the drug chamber.

$$\frac{dMt}{dt} = A\theta\Delta\pi\frac{C}{l},$$

where, *A* is the area of semi permeable membrane, $\Delta\pi$ is the osmotic pressure gradient, θ is the permeability of semipermeable membrane, and l is the thickness of semi permeable membrane. These basic equations are applicable to the osmotically driven controlled drug delivery devices. The saturated salt solution created a high osmotic pressure compared to that pressure required for pumping the suspension of active agent. Therefore, the rate of water entering into the salt chamber remains constant as long as sufficient solid salt is present in die salt chamber to maintain a saturated solution and thereby a constant osmotic pressure driving force is generated. The major problem associated with Rose-Nelson pumps was that the osmotic action began whenever water came in contact with the semipermeable membrane. This needed pumps to be stored empty and

water to be loaded prior to use. 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 by the production of a critical pressure at which the delivery orifice opens and releases the drug.

Further simplified variant of Rose-Nelson pump was developed by Higuchi and Theeuwes. This pump comprises a rigid, rate controlling outer semi permeable 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.

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 device through the delivery orifice. This process continues at a constant rate until the entire solid agent inside the tablet has been dissolved and only a solution filled coating membrane is left. These residual dissolved agents continue to be delivered at a declining rate until the osmotic pressure inside and outside the tablet are equal (Conley R *et al.*, 2006).

Elementary osmotic pump (EOP)

The was introduced in 1970s to deliver drug at zero order rates for prolonged periods, and is minimally affected by environmental factors such as pH or motility. The tablet consists of an osmotic core containing the drug surrounded by a semipermeable membrane laser drilled with delivery orifice. Following ingestion, water in absorbed into system dissolving the drug, and the resulting drug solution is delivered at the same rate as the water entering the tablet. The disadvantages of the elementary pump are that it is only suitable for the delivery of water soluble drugs (Good WR *et al.*, 1985; Okimoto K *et al.*, 1998).

Push–Pull Osmotic Pump (PPOP)

The two-layer push–pull osmotic tablet system appeared in 1980s. Push pull osmotic pump is a modified elementary osmotic pump through, which it is possible to deliver both poorly water-soluble and highly water soluble drugs at a constant rate. The push–pull osmotic tablet consists of two layers, one containing the drug and the other an osmotic agent and expandable agent. A semi permeable membrane that regulates water influx into both layers surrounds the system. It has a disadvantage that the complicated laser drilling technology should be employed to drill the orifice next to the drug compartment (Prescott LF *et al.*, 1989).

Controlled Porosity Osmotic Pump

A controlled porosity osmotic pump-based drug delivery system Unlike the elementary osmotic pump (EOP) which consists of an osmotic core with the drug surrounded by a semipermeable membrane drilled with a delivery orifice, controlled porosity of the membrane is accomplished by the use of different channeling agents in the coating. The CPOP contains water soluble additives in coating membrane, which after coming in contact with water; dissolve resulting in an in-situ formation of a micro porous membrane. Then the resulting membrane is substantially permeable to both water and dissolved solutes and the mechanism of drug release from these system was found to be primarily osmotic, with simple diffusion playing a minor role. Drug delivery from asymmetric membrane capsule is principally controlled by the osmotic pressure of the core formation. In-situ formed delivery orifice in the asymmetric membrane in mainly responsible for the solubilization in the core for a drug with poor water solubility (Rastogi SK *et al.*, 1995).

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. Varying the thickness as well as the area the semipermeable membrane can control release of drug. This system is useful to provide pulsated release (Higuchi T *et al.*, 1973).

Telescopic capsule for delayed release

This device consists of two chambers, the first contains the drug and an exit port, and the second contains an osmotic engine. A layer of wax like material separates the two sections. To assemble the delivery device, the

desired active agent is placed into one of the sections by manual or automated fill mechanism. The bilayer tablet with the osmotic engine is placed into a completed cap part of the capsule with the convex osmotic layer pointed in to the closed end of the cap and the barrier into the closed end of the cap and the barrier layer exposed towards the cap opening. The open end of the filled vessel is fitted inside the open end of the cap, and the two pieces are compressed together until the cap, osmotic bilayer tablet and vessel fit together tightly. As fluid is imbibed the housing of the dispensing device, the osmotic engine expand and exerts pressure on the 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 (Higuchi T *et al.,* 1973; Rose S *et al.,* 1955).

OROS-CT

OROS-CT (Alza corporation) 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. Incorporation of the cyclodextrin-drug complex has also been used as an approach for delivery of poorly water soluble drugs from the osmotic systems. Ex. Sulfobutylether-Bcyclodextrin sodium salt serves as a solubilizer and osmotic agent (Arora S *et al.,* 2006).

Sandwiched Osmotic Tablets (SOTS)

In this a tablet core 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 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 (Prescott LF *et al.,* 1989).

Longitudinally compressed tablet (LCT) multilayer formulation

The LCT multilayer formulation is the advanced design. As with the push-pull system it consists of an osmotic push layer and can be configured to contain several drug layers. The opinion of multiple drug layers provides increased flexibility and control over the pattern of release of medication from the system, as opposed to the single layer used in the push-pull system, which can deliver a drug only in a zero order fashion. For example, two drug layers could be formulated with different drug concentration to provide modulation in the release rate profile. As with the push-pull formulation, water is absorbed through the exposed semipermeable tablet shell, expanding the push compartment and releasing the drug primarily through the first compartment through the laser drilled orifice at a predetermined controlled rate. After most of the drug release begins from the second compartment at a different rate. Varying the relative viscosity and hydrophilicity of the drug layer components can control the amount of mixing between the multiple drug layers. This allows even greater flexibility to achieve the target release profile. The LCT multilayer formulation can also be formulated with different drugs in different layers to provide combination therapy(Rao BS *et al.,* 2001).

Pulsatile delivery system

Pulsatile systems are gaining a lot of interest as they deliver the drug at the right site of action at the right time and in the right amount, thus providing spatial and temporal delivery and increasing patient compliance. These systems are designed according to the circadian rhythm of the body. The principle rationale for the use of pulsatile release is for the drugs where a constant drug release, i.e., a zero order release is not desired. The release of the drug as a pulse after a lag time has to be designed in such a way that a complete and rapid drug release follows the lag time. This type of tablet system consist of core coated with two layer of swelling and rupturable coatings herein they used spray dried lactose and microcrystalline cellulose in drug core and then core was coated with swelling polymer cros carmellose sodium and an outer rupturable layer of ethyl cellulose. Pulsatile systems can be classified into single and multiple-unit systems. Single-unit systems are formulated either as capsule-based or osmosis based systems. Single-unit systems are designed by coating the system either with eroding/soluble or rupturable coating. In multiple-unit systems, however, the pulsatile release is induced by changing membrane permeability or by coating with a rupturable membrane (Sastry SV *et al.,* 1997).

Table 1. Classification of osmogents

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

Marketed products

Drug	Osmotic agent	Polymer osmogents	Formulation	Dose
Isradipine	Magnesium sulphate	Sodium carboxy methyl Cellulose	Push -Pull	5, 10 mg
Pseudoephedrine	Sodium chloride	HPMC	Elementary pump	60 mg IR, 180 mg CR
Nifedipine	Sodium bicarbonat	HPMC	Sandwiched Osmotic tablet	10, 20 mg
Chlorphen Iramine meleate	Sodium sulphate	MC	Elementary pump	4mg IR, 12mg CR
Verapamil	Potassium chloride	PVP	Push -Pull with time delay	180, 240 mg
Phenylpro Panolamine	Sodium chloride	PEO	Elementary pump	75 mg
Prazosin	Potassium chloride	HPMC	Push -Pull	2.5 - 5 mg

Fig 1. Osmotic drug delivery for solids

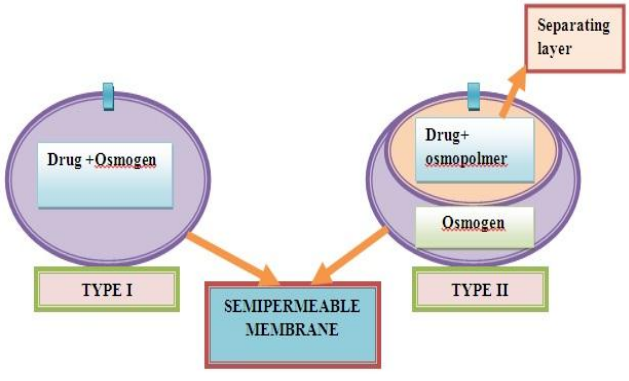


Fig 2. Osmotic drug delivery for liquids

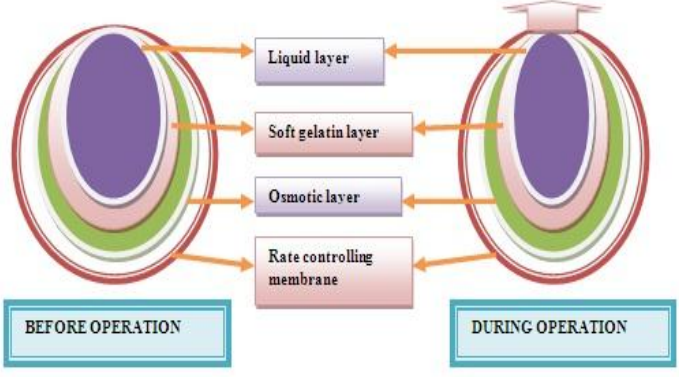


Fig 3. Rose-Nelson pump

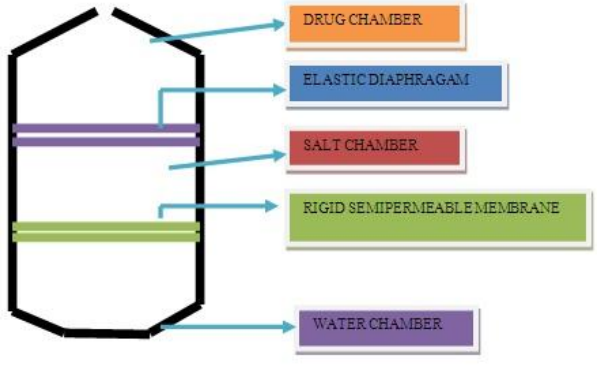


Fig 4. Higuchi -leeper pump

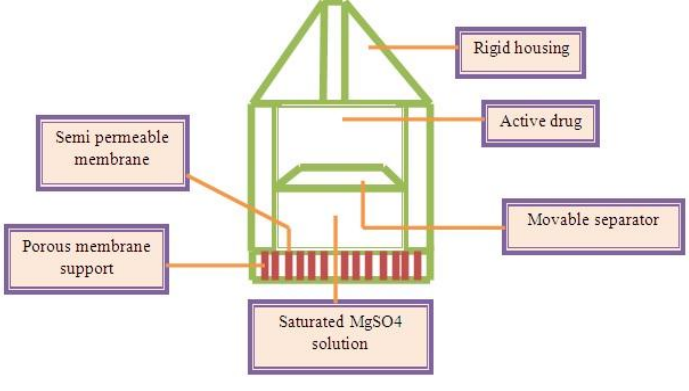


Fig 5. Higuchi and Theeuwes

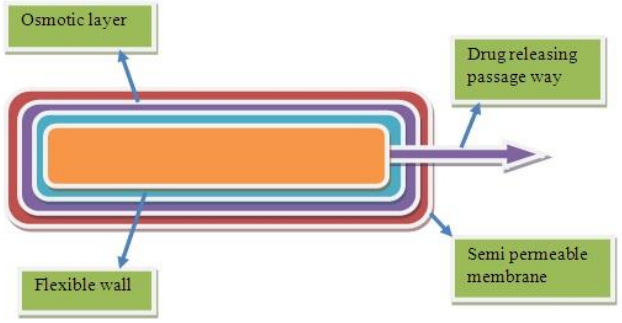


Fig 6. Elementary osmotic pump

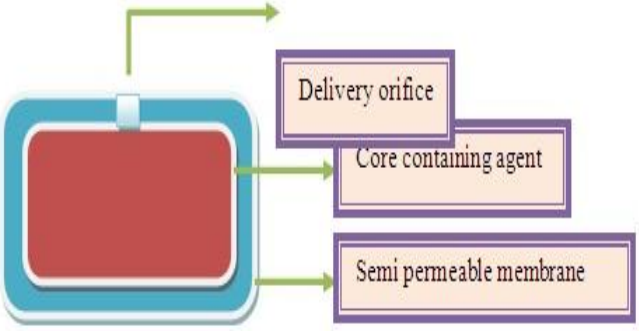


Fig 7. Push pull osmotic pump

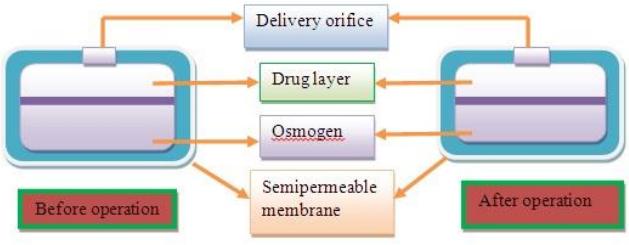


Fig 8. Controlled porosity osmotic pump

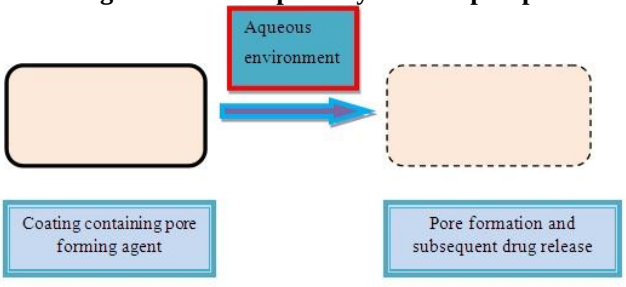


Fig 9. OROS-CT

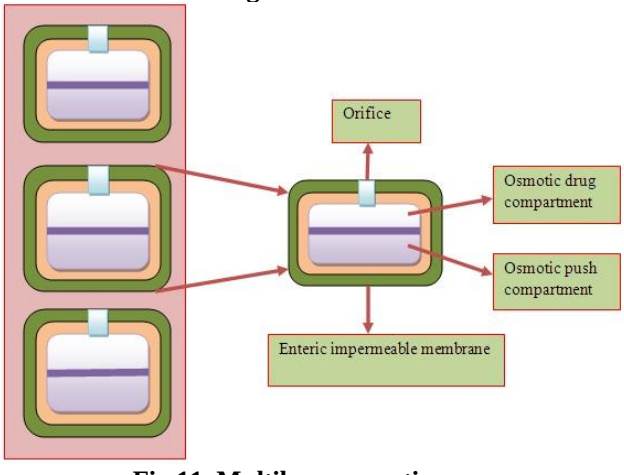


Fig 10. Sandwiched osmotic tablets

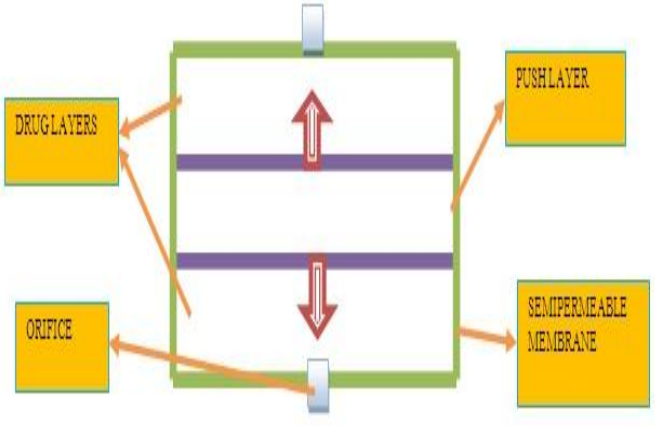


Fig 11. Multilayer osmotic pump

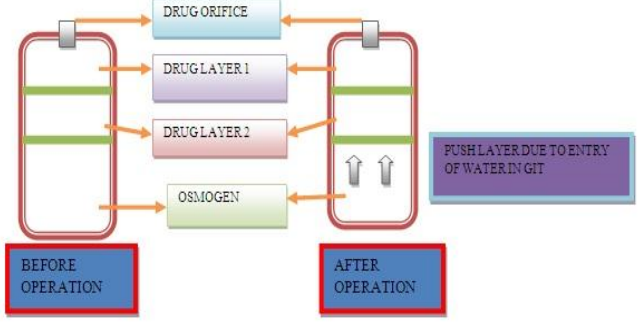
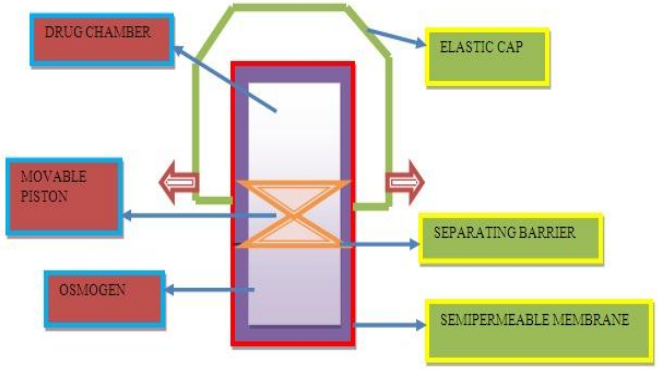


Fig 12. Pulsatile osmotic pump



CONCLUSION

In osmotic delivery systems, osmotic pressure provides the driving force for drug release. Increasing pressure inside the dosage form from water incursion causes the drug to release from the system. 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. Moreover, since efficacious plasma levels are maintained longer in osmotic systems, avoidance of trough plasma levels over the dosing interval is possible. However, a complex manufacturing process and higher cost compared with conventional dosage forms limit their use. Although not all drugs available for treating different diseases require such precise release rates, once-daily formulations based on osmotic principles are playing an increasingly important role in improving patient compliance.

Therefore, most of the currently marketed products are based on drugs used in long-term therapies for diabetes, hypertension, attention-deficit disorder, and other chronic disease states. 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.

ACKNOWLEDGEMENT

The authors are grateful to our respected Mr.Lakshmana Reddy and Mr. Manohar Reddy, the Chairmans of Jangoan and Trinity College of Pharmaceutical Sciences for providing necessary facilities to do this work.

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