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Review Article

An overview of Osmotic Drug Delivery System: An update review

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Abstract: The pharmaceutical industry has faced several marked challenges in order to bring new chemical entities (NCEs) into the market over the past few decades. Various novel drug delivery approaches have been used as a part of life cycle management from which Osmotic drug delivery systems look the most promising one. After discussing the history of osmotic pump development, this article looks at the principles, advantages and disadvantages of osmotic drug delivery systems. Then, the basic components of osmotic pump and factors affecting the design of oral osmotic drug delivery systems are discussed in detail. In the later part of the manuscript, various types of osmotic pumps available in the market and evaluation methods for osmotic drug delivery systems are discussed in detail.

Keywords: Osmotic Drug Delivery Systems, osmotic pump, semi-permeable membrane.

Introduction

During the past few decades, significant advances have been made in the area of novel drug delivery systems especially in the disciplines of biopharmaceutics, pharmacokinetics (PK) and pharmacodynamics (PD). In a typical conventional therapeutic regimen, the drug dose and dosing intervals are optimized to maintain drug concentration within the therapeutic window, thus ensuring efficacy and minimizing toxic effects. Generally, it was observed that dosing more than once or twice daily greatly reduces patient compliance. Thus, considerable attention has been made on the development of novel drug delivery system which provides the controlled release over a time in recent years. In addition, an existing drug molecule or drug therapy can get a new life by increasing its market value competitiveness and patent life by development of novel drug delivery systems.

There are a number of design options available to control or modulate the drug release from a dosage form. Generally, in order to formulate controlled oral drug delivery system, matrix, reservoir or osmotic systems are utilized. In a matrix system, the drug is embedded in polymer matrix and the release is controlled by partitioning of drug into the polymer matrix and the release medium which is generally dissolution medium. In contrast to matrix system, reservoir systems consist of a drug core, which is surrounded or coated by the rate controlling membrane. There are various factors such as pH, presence of food and other physiological factor can affect the drug release from these conventional controlled release systems. Osmotic drug delivery system is based on the principle of osmotic pressure for the delivery of drug. The major advantage of this type of system is that the drug release is independent of pH and other physiological parameters to a large extent. Thus, it makes possible to modulate the release characteristic by optimizing the properties of drug and system (Thombre *et al.,* 2004).

History:

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 make them valuable presence in the market. The very first and foremost drug delivery system that utilized the principles of osmotic pressure was developed by Australian pharmacologist Rose and Nelson in 1955. Two implantable osmotic pumps were developed by them; one that delivered 0.02 mL/day for 100 days and another that delivered 0.5 mL/day for 4 days. These both were used in pharmacological research (Santus and Baker, 1995). In 1971, another osmotic system which was very similar in its operation to that of Rose and Nelson's system was developed by Stolzenberg. But, both of these systems were used only in laboratory scale research. Thus, it had limitation on practical utilization in large scale production. In the 1970s, a series of variations of the Rose-Nelson pump were proposed by Higuchi and Leeper. From that time, many of the modifications have been invented which enable controlled delivery of almost all drugs. Theuwes invented elementary osmotic pump in 1972. Alza corporation of the USA was first to develop an oral osmotic pump and since today, they are the leaders in the field of osmotic pump drug delivery systems with a technology named OROS.

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Beginning in the 1980s and into the 1990s, Alza developed a family of osmotic pump capsules (e.g., Oros®) for controlled release of drugs in the GI (gastro-intestinal) tract, and one of their first patents issued in 1974. Felix Theeuwes, Liang Dong, Guohua Chen, Zhongli Ding and Lothar Kleiner at Alza were major contributors to the development of the various oral and implanted (Duros®) osmotic delivery systems which were under development in the 1990s. Prepared oral capsules gave a zero order, flat PK within the enteric-colonic tract, and some could be timed to release in various regions of the GI tract (Hoffman, 2008). The elementary osmotic pump was developed by Alza under the name OROS®, and has been commercialized for a number of drugs. The first product was Osmosin® (controlled release indomethacin) but it was withdrawn a year after launching due to its side effects. After that, a number of products were followed, leading to the launching of the blockbuster, billion-dollar product-controlled-release nifedipine (Procardia XL in the United States, Adalat CR in Europe). Related products include Acutrim® (phenylpropanolamine), Minipress XL® (prazosin), and Volmax® (salbutamol). There are number of other drugs in late-stage development, that includes glipizide, diltiazem, verapamil, gemfibrozil and isradipine. There are some products in clinical research such as Cognex CR (for tacrine delivery for treatment of Alzheimer's disease), OROS hydromorphone (for hydromorphone delivery for treatment of chronic pain), OROS methylphenidate (for methylphenidate delivery for treatment of attention deficit hyperactivity disorder) and Dilantin OROS (for phenytoin delivery for treatment of elileptic seizures) (Verma *et al.,* 2000). Some of the other formulations and delivery techniques were used in the past including iontophoresis of tacrine hydrochloride (Patel *et al.,* 2016a; Patel *et al.,* 2015, 2016b), intranasal delivery of tacrine hydrochloride (Jogani *et al.,* 2008; Jogani *et al.,* 2007), iontophoretic delivery of hydropmorphone (Padmanabhan *et al.,* 1990) and self-emulsifying drug delivery systems of phenytoin (Atef and Belmonte, 2008) etc. Researchers have also developed controlled porosity osmotic pump tables of diclofenac sodium for treatment of pain and also used design of experiments for optimization (Edavalath *et al.,* 2011). Researchers have used various formulation and delivery systems such as solid lipid nanoparticles (Liu *et al.,* 2010; Liu *et al.,* 2011), ethosomes (Jain *et al.,* 2015b, 2016) and iontophoresis (Kigasawa *et al.,* 2009) for delivery of diclofenac sodium. Researchers have also reported self-emulsifying osmotic pump tablet development of lipophilic drugs such as carvedilol; it is an additional development for optimum delivery of carvedilol apart from solid lipid nanoparticles (Shah *et al.,* 2014, 2015) and solid dispersions (Potluri *et al.,* 2011; Shamma and Basha, 2013) reported earlier. There are some reported review articles in the literature for osmotic drug delivery those can be referred by the interested readers for usage of osmotic drug delivery systems for drug delivery. Below is the list of some of the marketed products:

Table 1. List of some of marketed products based on Osmotic Drug Delivery Systems.

Product Name	Drug	Design	Dose
Acutrim	Phenylpropanolamine	Elementary pump	75 mg
Alpress LP	Prazosin	Push –Pull	2.5 - 5 mg
Cardura XL	Doxazosin	Push –Pull	4, 8 mg
Covera HS	Verapamil	Push -Pull with time delay	180, 240 mg
Ditropan XL	Oxybutinin chloride	Push -Pull	5, 10 mg
Dynacirc CR	Isradipine	Push -Pull	5, 10 mg
Efidac 24	Pseudoephiderine	Elementary Pump	60 mg IR, 180 mg CR
Efidac 24	Chlorpheniramine meleate	Elementary Pump	4 mg IR, 12 mg CR
Glucotrol XL	Glipizide	Push - Pull	5, 10 mg

Principles of Osmotic drug delivery system:

Principles of osmosis:

Osmosis is a physical phenomenon that has been extensively and thoroughly studied by scientists in various disciplines of science and engineering as well. Osmosis is a physical phenomenon that has been exploited by human beings since the early days of mankind. The overall idea of osmosis came up by early cultures, when they realized that salt could be used to desiccate foods for long-term preservation. They observed that in saline environments, most bacteria, fungi, and other potentially pathogenic organisms become dehydrated and die or become temporarily inactivated because of osmosis only. Previously, natural materials were used by early researchers to study the mechanism of osmosis, but from the 1960s, synthetic material came into the picture. Special attention has been given to osmosis through synthetic materials. Conventionally, osmosis can be defined as the net movement of water across a selectively permeable membrane driven by a difference in osmotic pressure across the membrane. This selectively permeable membrane allows only the passage of water, but does not allow the passage of solute molecules or ions.

Classification of osmotic processes:

Osmosis occurs as a result of transport of water across a selective permeable membrane from a region of higher water chemical potential to a region of lower water chemical potential. It occurs due to a difference in solute concentrations across

the membrane that allows passage of water only, but rejects the entry of solute molecules and/or ions. Thus, osmotic pressure (π) is the pressure which, if applied to the more concentrated solution, would prevent transport of water across the membrane (Achilli *et al.,* 2009). Forward osmosis (FO) is based on the osmotic pressure differential ($\Delta\pi$) across the membrane, and not on the hydraulic pressure differential (as in Reverse Osmosis), as the driving force for transport of water through the membrane. Pressure retarded osmosis (PRO) can be defined as an intermediate process between FO and RO, where the hydraulic pressure is applied in the opposite direction of the osmotic pressure gradient which is similar to RO and the net water flux is still in the direction of the concentrated draw solution which is similar to FO. Thus, it can be viewed as an intermediate process between FO and RO. Below equation describes water transport in FO, RO, and PRO which is given below (Lee *et al.,* 1981):

$$J_w = A(\sigma\Delta\pi - \Delta P) \qquad \text{eq.(1)}$$

Where,

J_w = the water flux,
A = the water permeability constant of the membrane,
σ = the reflection coefficient, and
ΔP is the applied pressure.
For Forward osmosis (FO): ΔP is zero
For reverse osmosis (RO): $\Delta P > \Delta\pi$;
For Pressure retarded osmosis (PRO): $\Delta\pi > \Delta P$.

Selection of Draw solutions:

The driving force in the FO process is the concentrated solution on the permeate side of the membrane. There are many different terms that can be used to name this solution includes draw solution, osmotic agent, osmotic media, driving solution, osmotic engine, sample solution, or just brine. During the selection of a draw solution, the main criterion is that it must have a higher osmotic pressure than the feed solution. The selection of a suitable process for re-concentrating the draw solution after it has been diluted in the FO process is another most important criterion in some applications of FO. Generally, NaCl solution is used as it has high solubility. Another advantage of using NaCI is its simplicity to re-concentrate to high concentration with RO without any risk of scaling (Cath *et al.,* 2006). Generally, the osmotic pressure difference across the active layer is much lower than that of the bulk osmotic pressure difference in these processes. Thus, it results in much lower water flux than that of expected. The resultant lower water flux is often attributed to several membrane-associated transport phenomena.

Advantages and Disadvantages of Osmotic drug delivery system:

Advantages of Osmotic drug delivery system:

Osmotic drug delivery system offers several advantages over other types of drug delivery system as following:

- A zero-order drug release profile can be achieved after an initial lag time.
- Reduction in side effects.
- Delayed or pulsed type of drug delivery can be achieved if desired.
- Drug release is totally independent of physiological parameters such as gastric pH and hydrodynamic condition.
- Well characterized and predictable release profile.
- Release mechanisms are not dependent on drug.
- High degree of in-vitro and *In vivo* correlation can also be achieved.
- The rationale for this approach is the presence of water in G.I.T. which is relatively constant, which can be viewed as at least in terms of the amount required for activation and controlling osmotically base technologies.

Disadvantages of Osmotic drug delivery system:

- Costly development and manufacturing.
- If the coating process is not performed well and loss of its control, may lead to a risk of film defects, resulting in failure and thus dose dumping may be observed.
- Size of the hole (delivery orifice) is always a critical step and impact on overall performance of drug delivery system.

Basic Component of Osmotic Pumps:

There are three major components of osmotic pumps: drug, osmotic agent and semi permeable membrane.

Drugs:

Selection of drug is the most important criterion in the osmotic drug delivery system as it ultimately affects the overall performance of drug delivery system. Following are some of the characteristics of an ideal drug for osmotic drug delivery system:

- Short biological half-life (about 2-6 hrs)
- High potency drugs that are required for prolonged treatment so, generally drugs which are used in chronic treatment are good candidates for osmotic drug delivery system.

Osmotic agents:

Osmogents can be either inorganic or organic in nature. In some cases where a drug is water soluble, it may serve the purpose of an osmogent itself. Some of the inorganic water soluble osmogents include magnesium sulphate, sodium chloride, sodium sulphate, potassium chloride and sodium

bicarbonate. Some of organic polymeric osmogents are sodium carboxymethyl cellulose, hydroxy propylmethyl cellulose, hydroxy ethylmethyl cellulose, methyl cellulose, polyethylene oxide and polyvinyl pyrollidine.

Table 2. Osmotic Pressure of Saturated Solutions of Common Pharmaceutical Solutes (Verma *et al.,* 2000).

Osmotic Compound or Mixture	Osmotic Pressure (atm)
Lactose-dextrose	225
Dextrose-fructose	450
Dextrose-fructose	450
Lactose-fructose	500
Sucrose-fructose	430
Mannitol-fructose	415
Sodium chloride	356
Fructose	335
Lactose-sucrose	250
Potassium chloride	245
Mannitol-dextrose	225
Dextrose-sucrose	190
Mannitol-sucrose	170
Sucrose	150
Mannitol-lactose	130
Dextrose	82
Potassium sulfate	39
Mannitol	38
Sodium phosphate tribasic.12 H2O Sodium phosphate dibasic.7 H2O	36
Sodium phosphate dibasic.12 H2O	31
Sodium phosphate dibasic anhydrous	29
Sodium phosphate monobasic.H2O	28

Semi permeable Membrane:

The semi permeable membrane is also the most important factor to be considered in the formulation of osmotic pump. Semi permeable membrane have already been utilized in the medical industry, in nicotine patches and other drug delivery devises as well. The membrane must be sufficiently rigid so as to able to retain its dimensional integrity during the operation of the device. The most important feature of the membrane is that it should also be relatively impermeable to the contents of dispenser. Thus, osmogent should not be lost by diffusion across the membrane and the membrane must be biocompatible (Theeuwes and Yum, 1976). Some of the ideal properties of semi permeable membranes are as below-

- It should be made of material which is rigid enough- or possess sufficient wet strength and wet modulus in order to retain its dimensional integrity during the operational lifetime of the device.
- The membrane must exhibit sufficient water permeability to retain water flux rate in the desired range.
- Finally, the membrane must also be biocompatible.

Materials for semi permeable membrane:

Generally, the semi permeable membranes consist of a thin film of polymeric material which is about one micrometer thick. These membranes should have high water permeability and a high degree of semi permeability- allowing water transport at the higher rate than the transport of dissolved ions. It should be rigid enough and should be stable over a wide range of pH and temperatures with good mechanical integrity. There are mainly two major groups of polymeric materials that possess the required qualifications to produce satisfactory membranes for osmosis and reversed osmosis: Cellulose Acetate (CAB) and Composite Polyamide (CPA).

Cellulose Acetate Membrane:

CAB membrane is usually made out of a blend of cellulose diacetate and triacetate. Membranes are prepared by casting a thin film acetone-based solution of cellulose acetate polymer with swelling additives onto a non-woven polyester fabric. Then, it is kept in a cold bath and again exposed to a high temperature in order to complete the process. The preparation by this method improves the semi permeability of the membrane. By this method, the final membrane is obtained which has a dense surface layer. Due to this dense layer, it does not allow the permeation of the salt whereas the membrane film is spongy and porous and has high water permeability. Variation in temperature and duration of the annealing step during the preparation can control the salt rejection and water flux.

Composite Polyamide Membrane:

Manufacturing of these membranes involves two steps: The first step is to cast a polysulfone support layer onto a non-woven polyester fabric which is very porous and not semi permeable itself. In the second step, interfacial polymerization is carried out to allow to form on the polysulfone substrate which is created in the first step by interfacial polymerization of monomers containing amine and carboxylic acid chloride functional groups. Composite polyamide membranes are advantageous compare to cellulose acetate membranes by higher water flow and lower salt passage. They are also stable over a wider pH range then the any other type of membranes. Sensibility for free chlorine is one of the major drawbacks of composite polyamide membranes, whereas; cellulose acetate membranes are able to tolerate some of them.

Factors to be considered in the design of Osmotic drug delivery systems:

- Physicochemical, pharmacokinetic, and pharmacodynamic properties of the drug.
- The anatomic and physiologic characteristics of the GI tract.
- Physicochemical characteristics and the drug delivery mode of the dosage form to be designed.

Solubility:
Solubility is the most important factor affecting the design of drug delivery because the delivery rate of a drug from an osmotic pump depends to a large extent on the solubility of drug at saturation (Jain *et al.,* 2015a). Thus, the drugs having water solubility in the range 50–300 mg/mL are good candidates for osmotic delivery. By modulating the solubility of these drugs within the core, effective and desired release patterns can be obtained. Kinetics of osmotic drug release is directly related to the solubility of the drug within the core.

Below are some of the approaches used to deliver drugs having extremes of solubility are:

Co-compression of drug with excipients:
For the drugs which have high water solubility, incorporation of sodium chloride into the core tablet formulation to reduce the solubility of drugs possessing extreme high-water solubility is one of the approaches (e.g. Diltiazem*)*. Below are some of the solubility modulating agents which can be either:

- Surfactant (sodium dodecylsulfate)
- Complexing agent (sodium salicylate)
- Organic acid (succinicadipicacid) (e.g. Doxazosin)

Another way to modulate the drug solubility within the core thermodynamic properties different from the parent drug is use of polymer coated buffer components (e.g. Theophyline). For pulsatile delivery of drugs, co-compression of drugs along with solubility modulating agents can also be utilized (e.g. salbutamol+ NACL) (Zentner *et al.,* 1991).

Use of encapsulated excipients:
The solubility of the poorly water-soluble drug can be improved by incorporation of encapsulated excipients (pH-controlling excipient) within the capsule device. Another approach is to formulate mini-tablets which can be coated with a rate controlling membrane in order to prolong its availability within the core (Thombre, 1997).

Use of swellable polymers:
Swellable polymers can be utilized for osmotic delivery of drugs with poor aqueous solubility. The formulation mainly consists of a compartment containing the drug, swelling agents, and osmagents which is coated with a rate controlling membrane. Generally, swelling agents for this formulation used are vinyl pyrrolidone, vinyl acetate copolymer and polyethylene oxide. The drug is released at a relatively constant rate, thereby providing uniform rate of swelling of these polymers (Khanna, 1991).

Use of effervescent mixtures:
Use of effervescent mixture can be another approach for the delivery of poorly water-soluble drugs from osmotic drug delivery systems. After administration, the effervescent mixture containing the drug is delivered under pressure from the delivery orifice. Citric acid and sodium bicarbonate are widely used as effervescent agents.

Use of cyclodextrin derivatives:
Cyclodextrin forms inclusion complex when combined with the drug. Thus, incorporation of the cyclodextrin–drug complex can also be used for the delivery of poorly water-soluble drugs from the osmotic systems. Example includes (sulfobutylether-B-cyclodextrinsodium salt, (SBE)-B-CD) which serve as a solubilizer and osmotic agent as well (Okimoto *et al.,* 1999).

Resin modulation approach:
For highly water-soluble drugs, positively charged anion-exchange resin –poly (4 –vinyl pyridine) can be an effective means to deliver the drug from osmotic delivery system.

Use of alternative salt form:
The salt forms were found to be having optimum solubility and thus they are able to provide extended release for some drugs.

Use of crystal habit modifiers:
It is possible that the drug may exists in more than one crystal form with different aqueous solubility. In this case, usage of crystal modifying agents such as combination of hydroxyl methyl cellulose and hydroxyl ethyl cellulose could be beneficial.

Use of lyotropic crystals:
For osmotic delivery of poorly water-soluble drugs, use of lyotropic liquid crystals which are known as amphipathic compounds could help as well. The lyotropic liquid crystals are non-polymeric compounds, having the molecular weight in the range of 200–1500 (Hiltrop, 1994). They will form mesophases and swell in the presence of water. Natural phosphatides such as phosphatidyl-controlled choline (lecithin), phosphatidyl ethanol amine, phosphatidyl serine, phosphatidyl glycerol are widely used as lyotropic liquid crystals.

Use of wicking agents:
A wicking agent is dispersed throughout the composition; it enhances the contact surface area of drug with the incoming aqueous fluids. Colloidal silicon dioxide, PVP, sodium lauryl sulfate is wicking agents that are widely used (Verma *et al.,* 2002).

Osmotic Pressure:
The release rate of drug from an osmotic system is directly proportional to the osmotic pressure of the core formulation. It is always necessary that osmotic pressure gradient between inside the compartment and the external environment should be optimized in order to control rate of drug

release. In order to achieve and maintain a constant osmotic pressure, a saturated solution of osmotic agent in the compartment should be maintained.

Table 3. Type of Osmotic Agents and name

Type of Osmotic Agents	Names of Osmotic Agents
Water soluble salts of inorganic salts	Magnesium chloride or sulfate; lithium, sodium or potassium chloride; lithium, sodium or potassium sulfate; sodium or potassium hydrogen phosphate
Water soluble salts if organic acids	Sodium and potassium acetate, magnesium succinate, sodium benzoate, sodium citrate, sodium ascorbate
Carbohydrates	Arabinose, Ribose, Xylose, Glucose, Fructose, Galactose, Mannose, Sucrose, Maltose, Lactose, Raffinose
Water soluble amino acids	Glycine, leucine, alanine, methionine
Organic polymeric osmogents	Sodium carboxy methylcellulose, HOMC, hydroxyethylmethylcellulose, polyethylene oxide, carbopol, polyacrylamides

Size of Delivery orifice:
The drug release from the osmotic pump occurs from the small holes (may be one or more) called as orifice. The size of delivery orifice must be optimized for osmotic systems to provide constant and maintained drug release. If the size of delivery orifice is too small, the hydrostatic pressure within the core will be developed and it may lead to deformation of delivery system resulting into unpredictable drug release. Whereas if the size of delivery orifice is too large than it may lead to increased diffusion of drug through the orifice. There are various methods to create delivery orifice:

Laser drilling: The tablets are allowed to drop by gravity into the slots of the rotating feed wheel and are carried at a predetermined velocity to the passageway forming station.

Use of modified punches: In this method, the dosage form is pierced with the use of a piercing device.

Systems with passageway formed in situ: As discussed earlier, the system consists of a tablet core of the drug along with water-swellable polymer and osmotic agents, which is surrounded by a rate-controlling semi permeable membrane. When this tablet comes in contact with the aqueous environment, water is imbibed osmotically at a controlled rate and water swellable polymer expands. Due to expansion, the osmotic agent dissolves and increases the osmotic pressure inside the tablet resulting into expansion of rate-controlled of the partially hydrated core. Due to the expansion of core, a small opening at the weakest point in the membrane form at the edge of the tablet. From this little hole, the drug can be released.

Use of pore formers: In this method, water-soluble additives (known as leachable additives) are incorporated in the membrane wall. When these water-soluble additives come in contact with the water, they get dissolve and forms the pores in the membrane through which drug release can take place. As it was discussed earlier that the drug release from these types of system are independent of pH and follows zero-order kinetics. There are many water-soluble additives that can be used for this purpose such as: Dimethylsulfone, nicotinamide, saccharides, amino acids, sorbitol, pentaerythritol, mannitol, organic aliphatic and aromatic acids including diols and polyols, and other water-soluble polymeric materials. (22, 23)

Membrane types and characteristics:
Type and nature of the membrane is also an important criterion to be considered for the required drug release. The semi permeable membrane must be thick (200–300 mm) enough to withstand the pressure within the device osmotic system.

Following are some of the criteria to be considered while selecting the membrane:

Type and nature of polymer:
Polymer selection is also an important factor that affects the drug release from the osmotic delivery system. Thus, any polymer which is permeable to water but impermeable to solute is selected. Various polymers are available for this purpose:

- Cellulose esters: cellulose acetate, cellulose diacetate, cellulose triace-cellulose propionate, cellulose acetate butyrate
- Cellulose ethers: Ethyl cellulose and Eudragits®

Membrane thickness:
It was very well understood that the thickness of the membrane has a marked effect on the drug release from osmotic system. Membrane thickness is inversely proportional to the release of drug from osmotically controlled drug delivery system (Herbig *et al.,* 1995).

Type and amount of plasticizer:
Plasticizers (mostly low molecular weight diluents) are added in order to modify the physical properties and improve film-forming characteristics of polymers. They are capable of converting a hard and brittle polymer into a softer, more pliable material, and thus making it more resistant to mechanical stress. Their amount and type (ex. polyethylene glycols) will have different effect on the water permeation and mechanical properties of Cellulose Acetate (CA). In a reported study, Water permeability was found to increase due to formation of plasticizer channels with increase in the concentration of plasticizers.

Osmotic pumps:
Osmotic systems utilize osmotic pressure as driving force for controlled delivery of drugs. Elementary osmotic pump (EOP) consists of an osmotic core (containing drug with or without an osmagent) coated with a semi permeable membrane (SPM). The dosage form, once in contact with the aqueous fluids, water penetrates at a rate determined by the fluid permeability of the membrane and creates osmotic pressure in core formulation. This osmotic imbibition of water results in formation of a saturated solution of drug within the core, which is dispensed at a controlled rate from the delivery orifice in the membrane (Theeuwes, 1975). In general, a lag time of approximately 30-60 min is observed as the system needs to hydrate prior to zero-order drug delivery begins. Therefore, about 60-80% of drug releases at a constant rate. These systems are suitable for delivery of drugs having moderate water solubility (Theeuwes, 1975). There are various osmotic delivery systems available with various different modifications to achieve desired drug release and some of them are discussed below:

Elementary Osmotic Pump (EOP):
The elementary osmotic pump is a new and modified version of traditional osmotic pump. It is possible to deliver the drug by an osmotic process at a predetermined controlled rate visa two controls: semi permeable membrane and osmotic properties of formulation. The simplest elementary osmotic system is constructed by coating an osmotically active agent with the rate controlling semi permeable membrane. The membrane contains an orifice of critical size through which drug is allowed to release. When the dosage form comes in contact with aqueous fluids, the water imbibes at a rate determined by the fluid permeability of the membrane and osmotic pressure of the core formulation. This results in osmotic imbibitions of water from a saturated solution of drug within the core and then saturated solution of drug is dispensed at controlled rate from the delivery orifice in the membrane. It was observed that the 60 -80 % of drug is released at a constant rate from the EOP, a lag time of almost 30-60 minute is also observed in most of the cases because the system need hydration time before zero order delivery from the system begins (Theeuwes *et al.,* 1983).

Push Pull Osmotic Pump:
Push pull osmotic pump is a modification of above explained EOP. The major advantage of this system over EOP is that, it is possible to deliver both poorly water-soluble as well as highly water soluble drugs at a constant rate (Malaterre *et al.,* 2009). This system is similar as a standard bilayer coated tablet where one layer contains drug in a formulation of polymeric, osmotic agent and other tablet excipients. After the coating has been applied, a small hole is drilled through the membrane by a suitable method such as laser or mechanical drill on the drug layer side of the tablet (Malaterre *et al.,* 2009).

Osmotic Pump with Non-Expanding Second Chamber:
This system is also belongs to multi-chamber devices. The major difference from the above system is that it contains a non-expanding second chamber. The first chamber contains a biologically inert osmotic agent, such as sugar or a simple salt like sodium chloride, whereas the second chamber contains the drug. This phenomenon is useful in the cases where because in some of the drug leaves the oral osmotic devices a saturated solution and thus irritation of GI tract may occur. The device is useful for the delivery of relatively insoluble drugs.

Osmotic Bursting Osmotic Pump:
This system is very similar to an EOP system. But it differs from EOP because the delivery orifice is absent and size may be smaller in this system. When it is placed in an aqueous environment, water is imbibed and thus hydraulic pressure is built up inside. Due to increased hydraulic pressure inside, in order to release the pressure the wall will rupture and the drug is released to the outside of the environment. In order to control the drug release and to obtain desired drug release, the thickness as well as the area of the semi permeable membrane can be varied. This type of system is able to provide drug release in pulse manner.

Liquid Oral Osmotic System:
To deliver drugs as liquid formulations and combine the benefits of extended release with high bioavailability, it is made possible by Liquid OROS. They are of three types of Liquid OROS: L- OROS hard cap, L- OROS soft cap and Delayed liquid bolus delivery system consists ofa liquid drug layer, an osmotic push layer and a semi-permeable membrane coating (Wong *et al.,* 1995). To achieve pulsatile delivery of liquid drug, L OROS delayed liquid bolus drug delivery system can be utilized. Whereas, L-OROS hardcap or softcap systems are preferred to achieve drug delivery in a continuous manner.

Delayed Delivery Osmotic Device:
As the name suggests, the osmotic device inherently show lag time before drug delivery begins because of the semi permeable walls. Thus, the presence of lag time is usually cited as a disadvantage, but it can be advantageous where the delayed release of certain drug may be beneficial (For example: drugs for early morning asthma or arthritis).

Telescopic Capsule for Delayed Release:
There are two chambers in this device: the first chamber contains the drug and an exit port, whereas the second chamber contains an osmotic

engine. In order to separate these two chambers from each other, a layer of waxy like material are used. If desired drug release is delayed type, than 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. Thus, the net flow of environmental fluid driven by the pressure enter the reservoir is very low and consequently there is no drug release during that period of time.

OROS-CT:
For the drugs which are to be taken as once or twice a day, OROS-CT formulation can be used. In addition, it is possible for targeted delivery of drugs to the colon by the OROS-CT. In the formulation, it can be have a single osmotic agent or it can be comprise of as many as five to six push pull osmotic unit filled in a hard gelatin capsule. Once it comes in contact with the gastric fluids, gelatin capsule get dissolved. But, the enteric coating prevents entry of fluids from stomach to the system. Thus, it remains intact in the stomach.

Sandwiched Osmotic Tablets (SOTS):
In this type of a system, polymeric push layer is sandwiched between two drug layers with two delivery orifices. When it is placed in the aqueous environment, the middle push layer that contains the swelling agent will swell and finally the drug is released from the two orifices situated on opposite sides of the tablet. SOTS can be suitable for drugs prone to cause local irritation of the gastric mucosa.

Monolithic Osmotic System:
In the monolithic osmotic system, it has a simple water-soluble agent which disperses in polymer matrix. When the system come in contact with the aqueous environment, water imbibitions by the active agent takes place. This leads to rupturing of the polymer matrix capsule surrounding the drug. Thus drug liberation takes place to the outside environment. However, it was observed that this system fails if more then 20 –30 volumes per liter of the active agent is incorporated in to the device. It fails may be because of as above this level, significant contribution from the simple leaching of the substance take place (Verma *et al.,* 2002).

Osmat:
Osmat is a novel in-situ osmotically driven matrix system. It is based on the simple principle that upon entry of aqueous medium, the hydrophilic polymers swells and forms a semi permeable membrane in-situ followed by drug release takes from a matrix system containing an osmogen. Thus, Osmat is based on the combine properties of both matrix osmotic characteristics resulting in a quantum improvement in drug delivery from swellable matrix system. Thus, osmat is a simple, versatile, and easy to fabricate osmotically driven controlled drug delivery system based upon low cost technology.

Controlled Porosity Osmotic Pump:
This type of system can be made with single or multi compartment dosage form. In both the dosage form, the delivery system contains a core with the drug surrounded by a membrane which has an asymmetric structure, i.e. comprises a thin dense skin layer supported by a porous substructure. This membrane is formed by phase inversion process which can be controlled by the evaporation of a mixed solvent system.

Mechanism:
Upon coming in contact with the water, of water-soluble additive which are dispersed in the wall are leached from polymer materials that were permeable to water but yet remained insoluble. This process forms a sponge like structure which formed the controlled porosity walls and it was permeable to both water and dissolved drug agents. Rate of drug delivery can be controlled by the various factors such as:

- The water permeability of the semi permeable membrane,
- Osmotic pressure of the core formulation,
- Thickness and total surface area of coating.

As it can be seen that all of the above variables are under the control of the formulator and they do not vary under different physiological condition. Thus, they are independent upon physiological conditions and thus leading to the robust performance.

The rate of flow (dv/dt) of water into the device can be represented as following;

$$\mathbf{d_v / d_t = Ak / h (D_p\text{-}DR)} \qquad \text{eq.(2)}$$

Where, k = Membrane permeability,
A= Area of the membrane,
D_p= Osmotic pressure difference,
D_R =Hydrostatic pressure difference.

Evaluation Methods for Osmotic drug delivery systems:
***In vitro* Delivery Rate Measurements:**
There are number of methods available for the determination of in-vitro delivery rate of drug(s) from the osmotic drug delivery systems. In loosely woven mesh bags of nylon or polyethylene, osmotic pumps are placed and the bags are attached to a rod, which in turn is attached to a horizontal transfer arm connected to a vertically reciprocating shaker. The arms containing several systems are then positioned over either on test tubes or containers that already have a known amount of release media into it. The temperature of the medium is kept constant (37°C ± 0.5°C) by using a temperature-controlled water bath. Now, as the shaker is started, the systems are immersed in the release media and stirred vertically. After a

certain pre-fixed period (1–2 hr), the systems are removed from the first receptor container and then it is moved (either manually or automatically) to a second receptor container, and the stirring is continued. This same procedure continues until the systems are tested for a fixed period of about 12–24 hr depending upon dosage form and formulation. Now, each receptor solution is then analyzed for the drug content by suitable method. The release rate (mg/hr) can be determined by dividing the amount of drug in each container by the time (in hours) of the test interval. And thus, the cumulative amount released is determined by adding the amounts from the various intervals. As discussed earlier that the drug release from the osmotic system follows the zero-order release profile. Thus, using least squares method of analysis the cumulative amount of drugs released from the optimized system at different time intervals are fitted to zero order kinetics to find out whether the drug release from the systems provides a constant drug release pattern or not.

In vivo Delivery Rate Measurements

It was observed that the environment in the intestinal tract of the dog is very similar to that of human beings in terms of both pH and motility. Thus, the dogs have been used widely for *In vivo* delivery rate measurement of drug from the osmotically controlled oral drug delivery system. To establish *In vitro-In vivo* Correlation (IVIVC), gastrointestinal transit of an osmotic tablet is measured by radio labeling an intact osmotic tablet which is placebo osmosin tablets. It is monitored for the movement of the unit in the GI tract of young and old healthy volunteers using gamma scintigraphy technique.

Summary:

Over the past few decades, the pharmaceutical industry has faced several marked challenges in order to bring new chemical entities (NCEs) into the market. Furthermore, the cost of developing NCEs are rising and requires more than US$ 800 million just for one NCE. Life-cycle management of on-patent pharmaceuticals is very important to pharmaceutical companies as they are challenged to meet their growth expectations. Thus, the drug delivery technology can be the best alternative to the life cycle management by providing optimized products for already existing drugs in terms of enhanced systemic circulation and reduced side effects.

Thus as a part of life cycle management, novel drug delivery systems (NDDS) have been recognized as an attractive function for the pharmaceutical industry. Among various NDDS, osmotic pumps have grown and accepted widely from their use with laboratory animals to the most reliable controlled release systems for humans. As seen earlier that in osmotically controlled drug delivery systems, osmotic pressure is used for controlled delivery of active agent(s).

However, the osmotic technology is expensive as compared to simple conventional matrix tablets or capsules. But, it can be concluded that the cost is worth the value provided due to time dependent extended drug release profiles which can be translated into optimized *In vivo* profiles for especially drugs with short half-life. As exemplified by the number of products in the market and patents granted in the last few years, these systems also hold a major market share in the drug delivery products. In addition, the biggest advantage of this system is that the drug delivery from these systems, to a large extent, is independent of the physiological factors of the gastrointestinal tract. Thus, because of the unique advantages offered by the osmotic drug delivery systems, osmotic pumps form a class of their own among the various novel drug delivery technologies making their way on the market. So, it is possible to use these systems to deliver drugs of diversified nature at a pre-programmed and pre-determine rate by modulating formulation factors.

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