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Osmotic Drug Delivery System: An Overview

Shoaeb Mohammad Syed*, Farooqui Z, Mohammed M, Dureshahwar K, Farooqui M
Research Scholar Govt. College of Pharmacy Aurangabad 431005
*Email: ybccpsh@gmail.com

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Abstract

The aim of current review was to elaborate the osmotic drug delivery system for controlled release of drugs. The oral route is the most common and most acceptable route of drug administration. For treatment of chronic diseases repeated dose administration is required, the osmotic drug delivery system serve as a tool for control release of drugs in these condition and avoid the repeated administration. The present review illustrates the basics of osmotic drug delivery system, types with special focus on controlled porosity osmotic pump, mechanism of osmosis, ideal drug candidate, formulation techniques, various osmotic agents, pore formers, coating materials and marketed preparation based on osmotic drug delivery system. These parameters may be helpful in designing of dosage for modification in release of various drugs having problem in conventional form.

Keywords: *Osmosis, Osmotic pressure, Osmotic drug delivery, Controlled porosity osmotic tablet, Pore former, Semipermeable membrane.*

1. Introduction

1.1 Introduction to Osmotic Drug Delivery System

Oral ingestion is one of the oldest and most extensively used routes of drug administration, providing a convenient method of effectively achieving both local and systemic effects. Novel drug delivery systems (NDDS) are the key area of pharmaceutical research and development. The reason is relatively low development cost and time required for introducing a NDDS ($20-50 million and 3-4 years, respectively) as compared to new chemical entity (approximately $500 million and 10-12 years, respectively) [Gupta *et al.*2009]. Conventional drug therapy require periodic doses of therapeutic agents and also known to provide an immediate release of drug, in which one cannot control the release of the drug and effective concentration at the target site. The bioavailability of drug from these formulations may vary significantly, depending on factors such as physico-chemical properties of the drug, presence of excipients, various physiological factors such as the presence or absence of food, pH of the GI tract, GI motility.

The term controlled release implies a system that provides continuous delivery of the drug for a predetermined period over a long period of time with predictable and reproducible kinetics, and a known mechanism of release [Shargel *et al.*1999]. The system attempts to control drug concentrations in the target tissues or cells. Controlled release (CR) mostly overlaps the market because of more advantages than conventional dosage form like ease of administration, reduced dosing frequency and better patient compliance. The main goal of controlled drug delivery systems is to improve the effectiveness of drug therapies by prolonged or sustained release of the drug for an extended period of time.

Various pharmaceutical approaches have been made to design long acting dosage form to administer once a day formulation as controlled and sustained release systems to deliver the drug. In the recent years, pharmaceutical research has led to the development of several novel drug delivery systems (NDDS). The role of drug development is to take a therapeutically effective molecule with sub-optimal physicochemical and/or physiological properties and develop an optimized product that will still be therapeutically effective but with additional benefits.

Osmotic systems are the most reliable controlled drug delivery systems (CDDS) and can be employed as oral drug delivery systems. Osmotic pressure is used as the driving force for these systems to release the drug in a controlled manner. Osmotic pump tablet (OPT) generally consists of a core including the drug(s), an osmotic agent, other excipients and semipermeable membrane coat. Osmosis is an aristocratic phenomenon that seizes the attention for its exploitation in zero-order drug delivery systems. It acts as driven force for release of drug from dosage form. Osmotic tablet worked on the principle Osmosis i.e. movement of water across a selectively permeable membrane driven by a difference in osmotic pressure across the membrane. It is driven by a difference in solute concentration across the membrane that allows

passage of water, but rejects most solute molecules or ions. On the basis of this principle osmotic drug delivery gives better drug release, not depends on concentration of drug and better results than any other controlled release system. Controlled drug release systems attempt to sustain drug action at a predetermined rate by maintaining a relatively constant, effective drug level in the body with minimization of undesirable side effects.

In oral NDDS, the development of the Osmotic drug delivery system is a significant milestone for an innovative and highly versatile drug delivery system. Osmotic drug delivery systems (ODDS) differ from diffusion-based systems in that; the delivery of the active agent(s) is driven by an osmotic gradient rather than the concentration of drug in the device [Ende *et al.*2005]. Osmotic devices are most promising strategy based systems for controlled drug delivery. There are over 240 patented osmotic drug delivery systems**.** Osmotic drug delivery systems are unique in the sense that the delivery of drug(s) is not dependent / influenced by physiological variables within the GIT, these systems are adaptable to a number of drugs, with minor modifications and the delivery of drug(s) can be made. They are also known as GITS (gastro-intestinal therapeutic system) and now, different types of osmotic pumps, of various drugs, are available in the market to meet patients need and requirement. The oral osmotic pumps have certainly come a long way and a number of patents granted in the last few years make it presence felt in the market [Gupta *et al.*2009].

1.1.1 Advantage of Osmotic drug delivery system:

Os motic drug delivery system for oral use offer distinct and practical advantage over other means of delivery. The following advantages contributed to the popularity of osmotic drug delivery system.

1. They typically give a zero order release profile after an initial lag.
2. The release mechanisms are independent on drug concentration.
3. Sustained and consistent blood levels within the therapeutic window [Gohel *et al.*2009].
4. Reduced side effects.
5. Deliveries may be delayed or pulsed if desired.
6. Drug release is independent of gastric pH and hydrodynamic condition.
7. They are well characterized and understood.
8. Delivery rate is independent of agitation outside, including GI motility.
9. Enhanced bioavailability of drug.
10. Reduced interpatient variability [Bhatt *et al.*2004].
11. Release rate of drug is highly predictable and programmable [Ajay *et al.*2010].
12. Decrease dosing frequency.
13. Improved patient compliance [Ajay *et al.*2010].
14. Increased safety margin of high potency drugs [Rajitha & Mathew 2009].
15. Drug release from the OCODDSs exhibits significant *in vitro-in vivo* correlation [*IVIVC*] within specific limits.
16. It is possible to attain better release rates than those obtained with conventional diffusion based drug delivery systems. [Sharma S. 2008]

1.1.2 Disadvantage: [Gadwal *et al.*2010]

1. High Cost.
2. If the coating process is not well controlled there is a risk of film defects, which results in dose dumping.
3. Hole Size is critical in case of elemetry osmotic system.
4. Drug release from the osmotic systems is affected to some extent by the presence of food.
5. Retrieval of therapy is not possible in the case of unexpected adverse event
6. Rapid development of tolerance.

1.2 Historical Background:

The osmosis principle was first used in the design of drug delivery systems by Rose and Nelson. 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. First osmotic drug delivery concept was developed by Theeuwes in 1974 [Vincent *et al.*2009]. In 1975, Theeuwes further simplified the Rose-Nelson pump made by Alza Corporation of the USA and developed a system known as the elementary osmotic pump (EOP) and hold major number of patents and also marketed several products [Ajay *et al.*2010]. Further simplified variant of Rose-Nelson pump was developed by Higuchi and Theeuwes. They design tablet composed of tablet-core surrounded by a semipermeable membrane with a single passageway (orifice), the so-called elementary osmotic pump (EOP) [Higuchi & Leeper 1973].

Th e first two products indomethacin, Osmosin [Theeuwes *et al.*1983] and phenylpropanolamine, Acutrim TM, were launched in the 1980s. Osmosin (EOP) of Merk's had to be withdrawn from the market due to severe side effects such as GI irritation and perforation of the intestinal wall [Donnelly P.1980]. The controlled-porosity osmotic pump tablet concept was developed as an oral drug delivery system by Zentner *et al* (1985, 1991), Zentner and Rork (1990), Appel and Zentner (1991), and Mc Celland *et al.* (1991). Osmotically oral drug delivery system (OODS) development continued with two new OODS designs, the controlled-porosity osmotic pumps (CPOP) and the push–pull osmotic pumps (PPOP). The first CPOP was designed to decrease the risk of extremely

localised drug-induced irritation at the site close to the orifice, as seen in the case of Osmosin. The applicability of the OODS to poorly soluble drugs was targeted by using PPOP. Thus, nifedipine PPOP (Procardia XL) was one of the most successful drug delivery systems of the last century, marking the revival of the OODS.

1.3. Types of Osmotically Controlled Drug Delivery Systems: [Sharma S. 2008]

1.3.1. Single chamber osmotic **system:**

1.3.1.1. Elementary osmotic pump

1.3.2. Multi chambered osmotic pumps

1.3.2.1. Push-pull osmotic pumps

1.3.2.2. Sandwiched osmotic pump

1.3.2.3. Osmotic pump with non expanding second chamber

1.3.3. Specific types

1.3.3.1. Controlled-porosity osmotic pumps

1.3.3.2. Monolithic osmotic pumps tablet

1.3.3.3. Colon targeted Oral Osmotic System (Oros CT)

1.3.3.4. Osmotically Brusting Osmotic Pump

1.3.3.5. Asymmetrical Membrane Osmotic Tablet

1.3.3.6. Liquid Oral Osmotic System

1.3.3.7. Effervescent Osmotic pump Tablet

1.3.3.8. Multiparticulate Delayed-Release System (osmotic pellet)

1.3.3.9. Self Emulsified Osmotic Tablet

1.3.3.10. Telescopic capsule for Delayed-Release

1.3.1. Single chamber osmotic system:

1.3.1.1. Elementary Osmotic Pump

In 1974 Theuwes invented elementary osmotic pump. The elementary osmotic pump is a new delivery system for drugs which delivers the drug by an osmotic process at a controlled rate. Control resides in the: a) Water permeation characteristics of a semi permeable membrane surrounding the formulating agent b) Osmotic properties of the formulation.

Th is system contains osmotically active agent surrounded by the rate controlling semipermeable membrane. The device is formed by compressing a drug having a suitable osmotic pressure into a tablet using a tableting machine. The tablet is then coated with a semi permeable membrane, usually cellulose acetate, and a small hole is drilled through the membrane coating (size varies from 0.5 to 1.5 mm).The drilling may be done by mechanical drilling, laser drilling (CO_2 laser beam with wavelength of 10.6µ) [Lu Xu *et al*.2006].

When the dosage form exposed to the aqueous environment, the core imbibes water osmotically at a controlled rate, which is determined by the water permeability of the semipermeable membrane and by the osmotic pressure of core formulation. The volume of saturated drug solution delivered is equal to the volume of solvent uptake. The rate of solute delivery by the system is constant as long as the excess of solid is present inside the device but the rate decline parabolically towards zero order, once the concentration falls below saturation, which is dispensed at controlled rate from the delivery orifice in the membrane. Though 60-80 percent of drug is released at a constant rate from the Elementary osmotic pump devices (EOP), a lag time of 30-60 minute is observed in most of the cases as the system hydrates before zero order delivery from the system begins. These systems are suitable for delivery of drugs having moderate water solubility [Gadwal *et al.* 2010].

1.3.2. Multi chambered osmotic pumps

1.3.2.1. Push Pull Osmotic Pump: (PPOP)

The PPOP, which was developed by Alza Corporation, consists of two compartments separated by an elastic diaphragm (optional). The upper compartment contains the drug and is connected to the outside environment via a small delivery orifice. A polymeric osmotic agent is present in the lower compartment and has no delivery orifice. The drug layer accounts for 60–80% of the tablet weight, while the osmotic polymer layer accounts for 20–40%. When the device comes in contact with the aqueous environment, both the drug layer and the polymer layer imbibe water. As the lower compartment is devoid of any orifice, it expands and pushes the diaphragm into the upper chamber, thereby delivering the drug via the delivery orifice [Vincent *et al.*2009].

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 [Sharma S.2008]. Carbopol (around 20-40% wt of the tablet) is most commonly used polymer in push layer. This system also have disadvantage of localized release and higher cost.

1.3.2.2. Sandwiched Osmotic Tablets (SOTS):

It is composed of polymeric push layer sandwiched between two drug layers with two delivery orifices. When placed in the aqueous environment the middle push layer containing the swelling agent 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]

1.3.2.3. Osmotic pump with Non Expanding Second Chamber:

The second category of multi-chamber devices comprises system containing a non-expanding second chamber. 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. 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 [Herbig *et al* 1995].

1.3.3. Specific types

1.3.3.1. Controlled Porosity Osmotic Pump:

The pump can be made with single or multicompartment dosage form, in either form, the delivery system comprises 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. The membrane is formed by phase inversion process controlled by the evaporation of a mixed solvent system. Membrane is permeable to water but impermeable to solute and insensitive pore forming additive dispersed throughout the wall. When exposed to water, low levels of water-soluble additive are leached from polymer materials that were permeable to water yet remained insoluble. Then resulting sponge like structure formed the controlled porosity walls of interest and was substantially permeable to both water and dissolved drug agents.

The release rate from these types of systems delivery depends upon the factors are water permeability of the semi permeable membrane, coating thickness, level of soluble components in the coating, solubility of the drug in the tablet core, and osmotic pressure difference across the membrane, but is independent of the pH and agitation of the release media, rate of drug release and the osmotic pressure of the core formulation, thickness and total surface area of coating. All of these variable are under the control of the designer and do not vary under physiological condition, leading to the robust performance allued to above. The rate of flow dv/dt of water into the device can be represented as, [Zentner *et al* 1985]

$$dv/dt = Ak / h (Dp-DR) \quad \text{.....(1)}$$

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

1.3.3.2. Monolithic Osmotic System:

The monolithic osmotic system consists of a simple dispersion of water-soluble agent in polymer matrix. The drug particles are encapsulated by polymers. When the system comes in contact with the aqueous environment the water imbibitions by the active agents takes place rupturing the polymer matrix capsule surrounding the drug, thus liberating it to the outside environment. 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. These systems govern the zero order drug delivery kinetics. The principle energy is osmotic pressure [Zentner *et al.*1985].

1.3.3.3. Colon Targeted Oral Osmotic System (OROS-CT):

Th is system can use for once or twice a day formulation for targeted delivery of drugs to the colon. The system is coated with 5-6 enteric coating and push-pull osmotic units filled in hard gelatin capsule for targeted colonic drug delivery [Gupta *et al* 2009]. When gelatine capsule shell dissolves after coming in contact with GI fluids, the entry of fluid from stomach is inhibited by outer shell of the system and it dissolves after entering into intestine. The water imbibes into the core and push compartment will swell. At the same time, the flowable gel is formed which is pushed out via delivery orifice at predetermined rate [Theeuwes *et al*.1993].

1.3.3.4. Osmotically Brusting Osmotic Pump:

A controlled-release delivery system utilizing an osmotic bursting mechanism was invented by Baker. In this system delivery orifice is absent and size of orifice is small than elementary osmotic system (EOP). When it is placed in an aqueous environment, water is imbibed and hydraulic pressure is built up inside until the wall rupture and the contents 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 [Amir & Joseph 2002].

1.3.3.5. Asymmetrical Membrane Osmotic Tablet:

As ymmetric membrane capsules consist of a drug containing core surrounded by a membrane which has an asymmetric structure i.e. it has a relatively thin, dense region supported on a thicker, porous region. The capsule wall is made from a water insoluble polymer such as cellulose acetate unlike a conventional gelatin capsule; the asymmetric

membrane capsule does not dissolve immediately but provides prolonged release of the active ingredient incorporated in the capsule. [Bhanushali *et al.*2009]

1.3.3.6. Liquid Oral Osmotic System:

Li

quid OROS are designed to deliver drugs as liquid formulations and combine the benefits of extended release with high bioavailability. These systems are suitable for controlled delivery of liquid drug formulation including lipophillic self-emulsifying formulation (SEF). They are of three types: -

L OROS hard cap
L OROS soft cap
Delayed liquid bolus delivery system

Each of these systems includes a liquid drug layer, an osmotic engine or push layer and a semipermeable 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 [Verma *et al.*2002]. Alza has developed osmotic systems to deliver liquids. This technology allows the delivery of insoluble drugs in aqueous fluids and is reported to increase the permeability of the drugs [Kaushal & Garg 2003].

1.3.3.7. Effervescent Osmotic Tablet (EOT):

In this system, effervescent compound are incorporated into dosage form which react with acid in the outer environment produce the carbon dioxide. This gas expands and dispenses the precipitate drug and prevents the blockage of orifice .This system beneficial for poorly soluble drug at low pH may precipitate at the gastric pH and block the delivery orifice. Sodium bicarbonate is usually use in this system. [Xio dong *et al*.2006].

1.3.3.8. Multiparticulate Delayed-Release System:

In this system, pellets containing pure drug with or without osmotic agent are coated with a semi-permeable membrane like cellulose acetate. When this system comes in contact with the aqueous environment, water penetrates into the core and forms a saturated solution of soluble components. The osmotic pressure gradient induces a water influx, leading to rapid expansion of the membrane and formation of the pores. The release of osmotic ingredient(s) and the drug through these pores tend to follow zero-order kinetics. Schultz and Kleinebudde studied, lag time and dissolution rates which are dependent on the coating level and osmotic properties of the dissolution medium. [Schultz & Kleinebudde 1997].

1.3.3.9. Self Emulsified Osmotic Tablet:

In the case of slightly soluble or practically insoluble drugs, self-emulsifying agents have been added to the tablet-core composition. About 40% drugs are available which are poorly aqueous solubility. Self emulsifying system improves the bioavailability of drug, controlled release rate and make the plasma concentrations more stable by self emulsifying agent. It emulsifies the hydrophobic drugs. Typical surfactants such as poly oxyethylenated glyceryl recinoleate, polyoxyethylenated castor oil having ethylene oxide, glyceryl laureates, glycerol (sorbiton oleate, stearate or laurate), etc have been used to serve the purpose. [Khavare *et al*. 2010].

1.3.3.10. 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 [Sharma S. *et al* 2008].

As fluid is imbibed in 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, 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 [Gohel *et al*.2009].

1.4 Controlled Porosity Osmotic Pump Tablet (CPOP):

Controlled porosity osmotic pump is simplest form of osmotic pumps. The controlled-porosity osmotic pump tablet concept was developed as an oral drug delivery system by Zentner *et al* [1985].Controlled porosity osmotic pump tablet contains core. In the core, water soluble additives and drug which surrounded by a insoluble coating membrane, which has an asymmetric structure, i.e. comprises a thin dense skin layer supported by a porous substructure. Membrane is permeable to water but impermeable to solute and insensitive pore forming additive dispersed throughout the wall. When device is coming in

contact with aqueous environment dissolved water-soluble additive are leached out from membrane that was permeable to water. Then resulting sponge like structure formed (microporous membrane) the controlled porosity walls of interest and was substantially permeable to both water and dissolved drug agents [Thombre *et al* 1999]. Generally, materials producing from 5 to 95% pores with a pore size from 10A - 100µm. Ying-Ku Lin (2003) studied the release mechanism of drug with moderate to high solubility with various solubility modulators **[**Lin & Ho 2003].

Some of the pore-forming additives that can be used are sodium chloride, urea, and potassium chloride, mannitol, and sorbitol. The release rate of drug delivery from these types of systems has been reported to be dependent on the coating thickness, level of soluble components in the coating, permeability of the semi permeable membrane, solubility of the drug in the tablet core, and osmotic pressure difference across the membrane, total surface area of coating, but is independent of the pH and agitation of the release media. All of these variable are under the control of the designer and do not vary under physiological condition, leading to the robust performance allued to above [Verma *et al.*2002].

1.5 Theory of Controlled Porosity Osmotic Pump Tablet (CPOP)

1.5.1 Osmosis

Osmosis can be defined as spontaneous movement of a solvent from a solution of lower solute concentration to a solution of higher solute concentration through an ideal semipermeable membrane, which is driven by a difference in osmotic pressure across the membrane that permeable only to the solvent and impermeable to solute molecules or ions. The pressure applied to the higher-concentration side to inhibit solvent flow is called osmotic pressure. Osmotic pressure is the pressure which, if applied to the more concentrated solution, would prevent transport of water across the semipermeable membrane. [Martin *et al.*1993]

1.5.2. Principle of Osmosis

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.

$$\Pi = p\ c\ RT \quad \text{..... (2)}$$

Where, Π = osmotic coefficient of the solution
p = Osmotic pressure of concentration of solution
c = molar concentration of sugar in the solution
R = gas constant and
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 results in a constant zero order release rate of drug [Li & Jasti 2006].

The Van't Hoff equation presents a good means for calculating the osmotic pressures of solutes across perfect semipermeable membranes and is accurate for low solute concentrations. But if the membrane is not completely semipermeable and permits passage for solute along with solvent, the osmotic pressure calculated by utilizing vapour pressure measurements and by using the expression.

$$\Pi = RT/V \ln (P_0/P) \quad \text{..... (2)}$$

Where, P_0 = vapour pressure of pure solvent, P = vapour pressure of the solution,
V = the molar volume of the solvent.

1.5.3. Mechanism:

In controlled porosity osmotic system, drug release from semipermeable membrane controlled by the difference in osmotic pressure between the external fluid and drug-containing core of the dosage form (Tablet). The pump can be made with single or multi-compartment dosage form, in either form; the delivery system comprises a core with the drug surrounded by a membrane. Membrane is permeable to water but impermeable to solute and insensitive pore forming additive dispersed throughout the wall [Sharma S.2008].

The mechanism of drug release from COP tablet when exposed to water, low levels of water-soluble additive are leached from polymer materials that were permeable to water through the semipermeable membrane into the tablet core, dissolution of soluble components (including drug) in the core, and pumping of the solution out of pores in the membrane. The imbibitions of water through the membrane are driven by its thermodynamic activity gradient between the external medium, e.g., receptor solution or gastric / intestinal fluids, and the osmotic agent(s) in the core. Then resulting sponge like structure formed the controlled porosity walls of interest and was substantially permeable to both water and dissolved drug agents.

Dissolution of the soluble components within the core produces the activity gradient and establishes the osmotic pressure difference between the core and external environment. The

approximately constant dosage form volume means that the volume of drug solution delivered will be roughly equal to the volume of water imbibed within a given time interval. As water diffuses into the core, the volume of the imbibed water creates a hydrostatic pressure difference across the membrane, which forces the solution out through the pores in the coating. Therefore, the rate of drug delivery will be constant as long as a constant osmotic pressure gradient is maintained across the membrane, the membrane permeability remains constant, and, the concentration of drug in the expelled solution is constant. Sustained zero-order drug release can be achieved using asymmetric membrane devices while the concentration of dissolved drug within the fluid portion of the core remains constant. When the drug concentration in the core fluid falls below saturation, the release rate declines [Swarbrick *et al.*1991].

Rate of drug delivery depends upon the factors are water permeability of the semi permeable membrane and the osmotic pressure of the core formulation, thickness and total surface area of coating. All of these variable are under the control of the designer and do not vary under physiological condition. The rate of flow dv/dt of water into the device can be represented by the equation,

$$dv\backslash dt = A\, k\, \Delta \pi \backslash h \quad \ldots\ldots\ldots\ldots\ldots (3)$$

Where, dv\dt = water flow across the membrane of area A,

h = thickness, k = Membrane permeability in cm2, A = Area of the membrane, $\Delta \pi$ is Osmotic pressure difference.

Th is equation is strictly for completely permeable selective membrane that is membrane permeable to water but completely impermeable to osmotic agent [Herbig *et al* .1995].

1.6 Basic components of Osmotic systems

1.6.1. Drug:

Drug which have short biological half-life (2-6 hrs), highly potent 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, verapamil etc are formulated as osmotic delivery. [Sharma S. 2008]

1.6.2. Osmotic agent:

Osmotic agents are essential ingredient of the osmotid formulation. Osmotic components usually are ionic compounds consisting of either inorganic salts hydrophilic polymers or carbohydrates. Generally combinations of osmotic agents are used to achieve optimum osmotic pressure inside the system. Different type of osmogents can be used for such systems are categorized as water-soluble salts of inorganic acids like magnesium chloride or sulfate; lithium, sodium, or potassium chloride; sodium or potassium hydrogen phosphate; water-soluble salts of organic acids like sodium and potassium acetate, magnesium succinate, sodium benzoate, sodium citrate, sodium ascorbate; Carbohydrates like mannose, sucrose, maltose lactose; water-soluble amino acids and organic polymeric osmogents, etc [Gadwal *et al*.2010].

Polymeric osmogents are mainly used in the fabrication of osmotically controlled drug delivery systems and other modified devices for controlled release of relatively insoluble drugs. Osmotic pressures for concentrated solution of soluble solutes commonly used in controlled release formulations are extremely high, ranging from 30 atm for sodium phosphate up to 500 atm for a lactose-fructose mixture (Table 1). These osmotic pressures can produce high water flows across semipermeable membranes.

1.6.3. Semipermeable membrane:

An important part of the osmotic drug delivery system is the Semipermiable membrane. Therefore, the polymeric membrane selection is the key to osmotic delivery formulation. Any polymer that is permeable to water but impermeable to solute (drug and excipients) 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. [Jensen et al.1995]. Cellulose acetate is commonly used for semi permeable membrane. It is available in different acetyl content like 32%, 38% are widely used [Gohel et al. 2009].

The membrane must possess certain performance criteria such as: [Sharma S. 2008]

1. The membrane should be stable to both outside and inside environments of the device.
2. The material must possess sufficient wet strength (10-5 Psi) and wet modules so (10-5 Psi) as to retain its dimensional integrity during the operational lifetime of the device.
3. It must exhibit sufficient water permeability so as to attain water flux rates (dv/dt) in the desired range. The water vapour transmission rates can be used to estimate water flux rates (Table 2).
4. It must be sufficiently rigid so as to withstand the pressure within the device, to retain its dimensional integrity during the operational lifetime of the device.
5. The reflection coefficient (σ) or "leakiness" of the osmotic agents should approach the limiting value of unity. But polymer membranes must be more permeable to water.
6. It should also be relatively impermeable to the contents of dispenser so that osmogent is not lost by diffusion across the membrane [Jensen *et al* 1995].
7. It should be non- swelling [Gohel *et al*.2009].
8. It should be biocompatible [Gohel *et al* 2009].

1.6.3.1 Water vapours Transmission Rate (WVTR):

Water Vapour Transmission Rate (WVTR) measures the ability to transport moisture through a material of specified thickness or the rate at which water vapor will pass through a material under specified conditions and specimen geometry. The volume of water vapor that will pass through a unit thickness of material per unit area per unit time per unit barometric pressure WVTR is measured in grams per square meter (g/m^2) over a 24 hours period according to the US standard ASTM – E398. The test specimen is held such that it separates two sides of a test chamber. The "wet side" of the specimen is exposed to a high relative humidity atmosphere, while the "dry side" is subjected to a zero relative humidity atmosphere. Infrared sensors on the "dry side" detect the amount of water vapor present. Testing is complete when the concentration of water vapor in the dry side atmosphere is constant. [Khavare *et al* 2010]

1.6.4. Pore forming agents (Channelling agents):

These are the water-soluble components which play an important role in the controlled drug delivery systems. When the dissolution medium comes into contact with the semipermeable membrane it dissolves the channeling agent and forms pores on the semipermeable barrier (Fig 10). Then the dissolution fluid enters the osmotic system and releases the drug in a controlled manner over a long period of time by the process of osmosis. This agent develope controlled porosity or multiparticulate osmotic pumps. Pore forming agent makes a microporous membrane. The micro porous wall may be formed in situ by a pore former by its leaching during the operation of the system. Pore formers can be inorganic or organic and solid or liquid in nature [Ajay *et al*.2010].

Some examples pore formers are alkaline metal salts. Such as NaCl, NaBr, KCl, potassium sulfate, potassium phosphate etc. alkaline earth metal like $CaCl_2$, calcium nitrate. Carbohydrates such as sucrose, glucose, fructose, mannose, lactose, sorbitol, mannitol, and diols and polyols like polyhydric alcohole, dibutylphthalate, polyvinyl pyrrolidone. The volatile pore formers used were ethanol and butanol. The non-volatile pore formers used were glycerol and water. It should be non toxic, and on their removal, channels should be formed [Khavare *et al*.2010].

1.6.5. Plasticizers:

Plasticizers used in coating membrane also have a significant importance in the formulation of osmotic systems. It lowers the temperature of the second order phase transition of the wall or the elastic modules of the wall and also increases the workability. They can change visco-elastic behavior of polymers and these changes may affect the permeability of the polymeric films [Pandey *et al* 2010].

Some of the plasticizers used are as below: [Gadwal *et al*.2010]

1. Polyethylene glycols
2. Ethylene glycol monoacetate; and diacetate- for low permeability
3. Tri ethyl citrate
4. Diethyl tartarate or Diacetin- for more permeable films
5. dialkylphthalate, Trioctylphosphate,
6. Alkyl adipates, Acetate, Propionate, Glycolate.

1.6.6. Coating Solvent

For making polymeric membrane, suitable solvent should be used. There are various organic and inorganic solvent are available. Solvents should not be toxic, should not be alter the chemical nature of polymer, should be solubilise to polymer completely. Some examples of solvents are acetone, isopropyl alcohol, ethanol, methanol, carbon tetrachloride, water, ethyl acetate, cyclohexane, butyl alcohol. The mixture of solvent like, acetone-ethanol, methylene chloride-methanol, acetone-isopropyl alcohol, acetone-water, methylene choloride-methanol-water. **[**Pandey *et al*.2010]

1.7 Market Study

In the market, there are thirty-one products have been developed and marketed based on OODS technology. All these products are under the therapeutic areas: cardiovascular (35%), neurological (25%), seasonal (25%) and metabolic disorders (15%) [Verma *et al*.2004].These products have been mainly developed by two companies, the former Alza Corp., which was later acquired by Johnson & Johnson developed 20 products (53%), and Osmotica Pharmaceutical Corp., which was a spin-off company of Phoenix Inc., with 10 products (26%). Seven products are currently in the late development stage, of which three compounds are for pain management [Amabile *et al*.2006]. Now, two-fold increase in the OODS revenues in the past 5 years, reaching about 3 billion dollars worldwide annual sales. Thus, the OODS worldwide sales increased from about 3.0% of the modified-release forms in 2002 to 6.2% in 2007 (Top 300 worldwide sales) [Gupta *et al.*1999]. So, Osmotic drug delivery products are become more popular in the market. Marketed products are summarized in Table 5.

2. Conclusion

Osmotic drug delivery system can be a promising tool in oral drug delivery. Controlled porosity osmotic can be used for designing various formulations containing the osmotic agent, pore former and rate controlling membrane. Optimization of these parameters can control the release of drug

as per the time period require. By using this technique the release may be pulsed for the specific time in chronotherapy.

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