A Brif Review On Osmotic Drug Delivery System

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Abstract- *An oral push-pull system that can deliver drug for extended period of time has been developed and characterized. A bilayer osmotic drug delivery system was developed using a basic design consisting of an oral osmotic controlled push-pull pump system. This system require a preformed orifice for drug release, it contain semi-permeable membrane and water-soluble pore-formers in the coating membrane. When this system comes in contact with water, the flux forming agent get dissolve resulting in an in-situ formation of a microporous membrane. The push layer get contact with water and get swells and releasing the drug at a controlled rate. In case of drug which having short half-life the frequency of dose administration is more like three to four times a day. Hence, an attempt was made to develop a 24 hours extends the release of the drug at predetermined rate. This offer significant patient benefits by reducing the side effects, enhanced efficacy and also reduce the frequency or number of daily doses compared to conventional therapies.*

Keywords- Osmotic pump, Orifice, Push-pull system, osmotic agents, etc.

I. INTRODUCTION

Novel Drug Delivery System (NDDS)

An attractive niche is the novel oral drug delivery systems in recent years in the field of pharmacy. The drugs are to be delivered in suitable form meeting desirable criteria considering the importance of safety, efficacy and acceptability among other factors. This suitable form later is called as dosage form or drug delivery system (DDS).[1] Molecular interaction(s) in certain cells results in drug activity. It is thus necessary for the drug to reach somehow the site of action following administration (oral, intravenous, local, transdermal, etc.) at sufficient concentrations. The scientific field dealing with this issue is known as drug delivery. It essentially has the following aims: to deliver the drug at the right place, at the right concentration for the right period of time. The matter of concern is also that the development of new drugs alone is not sufficient to ensure progress in drug therapy so necessity is the innovation in drug delivery systems. Also there is relatively low development cost and time required for introducing a NDDS as compared to developing a new chemical entity. In the form of NDDS, an existing drug molecule can get a new life thereby, increasing its market value, competitiveness, and patent life. NDDS improves bioavailability, patient compliance by decreasing dosing frequency and convenient route of administration, increases duration of action and reduces side effects as well. Above all achieves targeting of drugs to specified sites thus later reducing side effects and achieving maximum efficacy.[2]

Among the various NDDS available in market, per oral controlled release (CR) systems hold the major market share.[3] CR delivery systems provide desired concentration of drug at the absorption site allowing maintenance of plasma concentrations within the therapeutic range thus later reducing dosing frequency. Majority of per oral CR dosage forms fall in the category of matrix, reservoir, or osmotic systems. The drug is embedded in a polymer matrix and the release takes place by partitioning of drug into the polymer matrix, also the release medium whereas reservoir systems have a drug core surrounded by a rate controlling membrane. Still factors like pH, presence of food, and other physiological factors affects drug release from conventional CR systems (matrix and reservoir). Osmotic systems utilize the principles of osmotic pressure for the delivery of drugs. Drug release from these systems is independent of pH and other physiological parameters to a large extent. The release characteristics probably can be modulated by optimizing the properties of drug and system.

Osmotic Drug Delivery System (ODDS)

Osmotically-driven systems have been evolved from being device-concepts that was primarily for the delivery of veterinary medicines, namely Rose-Nelson, Higuchi-Leeper and Higuchi-Theeuwes pumps. Using osmotic pressure as the energy source, the semipermeable membrane controls water inflow, generates hydrodynamic pressure inside the device and thus controls drug delivery. In the year 1974 with Theeuwes and Alza's co-workers designed tablet-core surrounded by a semipermeable membrane with an orifice I.e. elementary osmotic pump (EOP). In 1980 sindomethacin, Osmosin®[9] and phenylpropanolamine, AcutrimTM, were launched. Osmosin® was withdrawn from the market due to severe side-effects of GI irritation and perforation of the intestinal wall.[10-11] Due to these adverse events seen with the OODS formulations of indomethacin.[12-15] the use of OODS has for many years been associated with the amplified risk of stagnation of the dosage form in the GI tract. Despite these

events negatively affecting the reputation of these drug delivery systems, OODS development continued with two new OODS designs, the controlled-porosity osmotic pumps (CPOP) and the push-pull osmotic pumps (PPOP). The first of these was the CPOP, which 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. This system was the gold-standard treatment for the management of hypertension from 1990 to 1995.[16-18] Despite the relatively low incidence of safety events seen with Procardia XL®, there were continuous clinical controversies surrounding the risk of GI occlusions of this dosage form in patients with a certain disposition.[19-20] In the 2000s, a new drug product based on OODS technology was formulated to deliver methylphenidate to children (above the age of 6 years) with attention-deficit hyperactivity disorder (ADHD). These delivery systems were based on a new design, the push-stick osmotic pumps (PSOP), which combined immediate and sustained drug release phases. This system, Concerti TM, 20 seemed to mark the end of the controversies concerning good treatment compliance with the technology and demonstrated tolerability in children.[21] The history of the OODS reflects the difficulty in developing an innovative technology in the pharmaceutical field.[2] Osmotic drug-delivery systems suitable for oral administration typically consist of a compressed tablet core that is coated with a semipermeable membrane coating. This coating has one or more delivery ports through which a solution or suspension of the drug is released over time. The core consists of a drug formulation that contains an osmotic agent and a water swellable polymer. The rate at which the core absorbs water depends on the osmotic pressure generated by the core components and the permeability of the membrane coating. As the core absorbs water, it expands in volume, which pushes the drug solution or suspension out of the tablet through one or more delivery ports. The key distinguishing feature of osmotic drug delivery systems (compared with other technologies used in controlled-release formulations) is that they release drug at a rate that is independent of the pH and hydrodynamics of the external dissolution medium. The result is a robust dosage form for which the in vivo rate of drug release is comparable to the in vitro rate, producing an excellent in vitro/in vivo correlation. Another key advantage of the present osmotic systems is that they are applicable to drugs with a broad range of aqueous solubilities. Depending on aqueous solubility, the drug is released either as a solution or as a suspension. Of course, any drug released as a suspension must dissolve in the in vivo environment and overcome biological barriers before it becomes systemically available.[22] Drug release from osmotic dosage forms is independent of pH, ionic strength, agitation and other physiological factors within the gastrointestinal tract. These attributes minimize patient-to-patient variability and allow accurate prediction of in vivo performance from in vitro dissolution profiles.

Osmosis and its principle

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 that allows passage of water but casts off solute molecules or ions. The first osmotic effect was reported by Abbe Nollet in 1748. Later in 1877, Pfeffer performed an experiment using a 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 1866, Vant Hoff identified an underlying proportionality between osmotic pressure, concentration and temperature .He revealed that the osmotic pressure is proportional to the concentration and temperature and the relationship can be described by the following equation:

$\Pi = \phi cRT$

Where π=osmotic pressure, ϕ=osmotic coefficient, c=molar concentration ,R=gas constant , T=absolute temperature.

Osmotic pressure is a colligative property that depends on concentration of solute that contributes to osmotic pressure. Solutions of different concentrations having the same solute and the solvent system exhibit an osmotic pressure proportional to their concentrations. Thus a constant osmotic pressure, and thereby a constant influx of water can be achived by an osmotic delivery system that results in a constant zero order release rate of the drug.[22]

Basic Components of Osmotic Systems[23]

Drug

Drugs which have short biological half-life and which are used for prolonged treatment are ideal Candidates for osmotic systems. Various drug candidates such as Diltiazem HCl, Carbamazepine, Metoprolol, Oxprenolol, Nifedipine, Glipizide etc. are formulated as osmotic delivery.

Semipermeable membrane[23]

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[23]

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. Some of the compounds that can be used as osmagents are listed.

Table 1: List of Osmogents.

Category	Examples
Water-soluble salts of inorganicacids	Magnesium chloride or sulfate; lithium,sodium, or potassium chloride; lithium, sodium, or potassium sulfate; sodium or potassium hydrogen phosphate, etc.
Water-soluble salts of organicacids	Sodium and potassium acetate, magnesium succinate, sodium benzoate, sodium citrate, sodium ascorbate, etc.
Water-soluble amino acids	Glycine, leucine, alanine, methionine, etc.
Carbohydrates	Arabinose, ribose, xylose, glucose, fructose,galactose, mannose, sucrose, maltose, lactose, raffinose, mannitol.
Organic polymeric osmagents	Sodium carboxy methylcellulose, HPMC, hydroxyethyl methylcellulose, cross-linkedPVP, polyethylene oxide, carbopols, polyacrylamides, etc.

Flux regulators[23]

Delivery systems can be designed to regulate the permeability of the fluid by incorporating flux regulating agents in the layer. Hydrophilic substances such as polyethethylene glycols (300 -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[23]

A wicking agent is of either swellable or non-swellable nature. 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 act as wicking agents include colloidal silicon dioxide, kaolin, 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[23]

The pore forming 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 polyhydric alcohols and polyvinyl pyrrolidone can be used as pore forming agents.

Coating solvent[23]

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

alcohol, butyl alcohol, 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).

Plasticizers[23]

The plasticizers can change visco-elastic behavior of polymers and these changes may affect the permeability of the polymeric films. e.g. Polyethylene glycols, Ethylene glycol monoacetate; and diacetate- for low permeability, Tri ethyl citrate and Diethyl tartarate or Diacetin- for more permeable films.

Key Parameters That Influence The Design of Osmotic Controlled Drug Delivery Systems

Orifice size[23]

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. 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.

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 semipermeable coating: e.g. controlled porosity osmotic pump.

Solubility[23]

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 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.

Osmotic pressure[23]

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.

Semipermeable membrane[23]

Since the semipermeable 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.

Formulation Considerations[24] Formulation aspects

The delivery of agent from oral osmotic systems is controlled by the influx of solvent across the SPM, which in turn carries the agent to the outside environment. Water influx into EOP can be described by the following equation:

$$\frac{dv}{dt} = \frac{A}{h} Lp(\sigma \Delta \pi - \Delta p) \quad (1)$$

Where dv/dt is water influx, A and h are the membrane area and membrane thickness, respectively; Lp is mechanical permeability; σ is the reflection coefficient; and ΔΠ and Δp are the osmotic and hydrostatic pressure differences, respectively, between the inside and outside of the system. The general expression for the solute delivery rate, dM/dt, obtained by pumping through the orifice is given by:

$$\frac{dM}{dt} = \frac{dv}{dt} \cdot C \quad (2)$$

Where C is the concentration of compound in the dispensed fluid.

Reflection coefficient takes into account the leakage of solute through the membrane. A perfectly semi permeable membrane is selectively permeable to water only and does not allow solute to pass through it. Thus, in case of a perfectly semipermeable membrane, σ is close to unity. As size of the delivery orifice increases, hydrostatic pressure inside the system is minimized and ΔΠ >>Δp. Since, osmotic pressure of the gastro intestinal fluid is negligible as compared to that of core, Π can be safely substituted for ΔΠ. By replacing the product Lp σ, in equation (1), by a constant K and substituting equation (1) in equation (2), the following equation is obtained:

$$\frac{dM}{dt} = \frac{A}{h} K\pi C \quad (3)$$

The best possible way to achieve a constant release from osmotic systems is through proper selection and optimization of the SPM (To maintain the first three terms on the right hand side of the equation constant) and maintaining a saturated solution of drug within the core. As long as excess solid agent is present inside the system, both Π and C in equation (3) can be maintained at constant levels. Therefore, it is possible to obtain zero-order release rates from osmotic system by maintaining the terms in equation (3) constant.

Factors that affect the drug release from osmotic pumps

Solubility

The kinetics of osmotic drug release is directly proportional to the solubility of the drug within the core. Assuming a tablet core of pure drug, the fraction of core released with zero order kinetics is given by the following equation.

F(z} = 1-S/p equation (4)

Where, F(z) is the fraction released by zero order kinetics, S is the solubility of drug, and p is the density of the core tablets. Drugs with the solubility of less than 0.05 gm/cc would be released with more than 95% zero order kinetics according to equation (4). However, the zero order release rate would be slow according to equation (3), due to the small osmotic pressure gradient. Conversely, highly water soluble drugs would demonstrate a high release rate that would be zero-order for a small percentage of the initial drug load. Thus, the intrinsic water solubility of many drugs might preclude them from incorporation into an osmotic pump. However, it is possible to modulate the solubility of the drugs within the core, and thus, extend this technology for delivery of drugs that might otherwise have been poor candidates for osmotic delivery. Some of the approaches that have been used to deliver drugs having extremes of solubility are.

Co compression of drugs with excipients

Incorporation of excipients that modulate the solubility of drug within the core can be one approach to control the release of drugs from the osmotic systems. McClelland and coworkers reported[25,26] CPOP of a highly water-soluble drug, diltiazem hydrochloride (solubility more than 590 mg / ml at 37 C). Because of very high water-solubility, the majority of the drug fraction was released predominantly at a first-order rather than the desired zero-order rate. The solubility of diltiazem hydrochloride was reduced to 155 mg / ml by incorporation of sodium chloride (at 1M concentration) into the core tablet formulation. The modification resulted in more than 75% of the drug to be released by zero-order kinetics over a 14-16 h period.

Use of encapsulated excipients

Solubility of a poorly water-soluble drug, glipizide, was improved by incorporation of encapsulated excipients (pH-controlling excipients) within the capsule device. The solubility modifier (meglumine), in the form of mini-tablets, was coated with a rate controlling membrane to prolong its availability within the core. Thus, the solubility of glipizide was improved leading to its prolonged release from the device.[27,28]

Use of swellable polymers

Examples using this approach are reported in US patent no. 4,992,278 for carbamazepine, acetylsalicylic acid, theophyline and nifedipine. The formulation mainly consists of a compartment, containing the drug, swelling agents, and osmagents, coated with a rate controlling membrane. Vinylpyrrolidone /vinyl acetate copolymer and polyethylene oxide were used as swelling agents. Uniform rate of swelling of these polymers ensures that the drug is released at a relatively constant rate. Also, the pressure produced during swelling does not lead to rupture of the system. In addition, PPOP can also be utilized for delivery of drugs having either high, e.g. oxybutynin chloride, or low water solubility, e.g. glipizide.[29-32] Drug is released from the delivery orifice in the form of very fine dispersion ready for dissolution and absorption. Sandwiched osmotic tablets (SOTS) have also been utilized for osmotic delivery of water insoluble drugs, such as nifedipine.[33] The release profile from the tablets was found to be comparable with the commercially available push–pull osmotic system of the drug.

Use of effervescent mixtures

After administration, the effervescent mixture containing the drug is delivered under pressure through the delivery orifice in the membrane. This method of enhancing release of poorly water-soluble drug is reported in US patent no. 4, 036, 228.[34] In one of the examples, citric acid and sodium

bicarbonate were used as the effervescent couple for the delivery of acetyl salicylic acid. The formulation imbibes aqueous fluids across the membrane causing the couple to generate an effervescent solution that dispenses the drug in a suspension form.

Use of cyclodextrin derivatives

Incorporation of the cyclodextrin–drug complex has also been used as an approach for delivery of poorly water-soluble drugs from the osmotic systems.

Resin modulation approach

Release of a highly water-soluble drug, diltiazem hydrochloride from a CPOP was modulated effectively using positively charged anion-exchange resin, poly (4-vinyl pyridine).[35]

Use of alternative salt form

Hydrochloride salt used in commercial formulations of oxprenolol was found to have high water solubility (70% w/v) making it difficult to achieve extended zero-order delivery from osmotic systems. It was replaced by the less soluble succinate salt.

Use of crystal habit modifier

If the drug exists in more than one crystal form, each having different aqueous solubility, it is beneficial to include a crystal modifying agents. One such example is reported in US patent no. 5, 284, 662,[36] wherein a slightly soluble drug, carbamazepine, along with crystal modifying agents (combination of hydroxymethyl cellulose and hydroxyethyl cellulose) and other excipients was formulated in the form of osmotic pumps that were able to provide approximately zero-order release for the desired period of time.

Use of wicking agents

Inclusion of wicking agents in the osmotic formulations has also been reported as an approach for poorly water-soluble drugs e.g. nifedipine.[37]

Osmotic pressure

It is evident that the release rate of a drug from an osmotic system is directly proportional to the osmotic pressure of the core formulation. For controlling the drug release from thesesystems, it is important to optimize the osmotic pressure gradient between inside compartment and the external environment. It is possible to achieve and maintain a constant osmotic pressure by maintaining a saturated solution of osmotic agent in the compartment.[38] If a drug does not possess sufficient osmotic pressure, an osmagent can be added in the formulation.

Delivery orifice

Osmotic delivery systems contain at least one delivery orifice in the membrane for drug release. The size of delivery orifice must be optimized in order to control the drug release from osmotic systems. If the size of delivery orifice is too small, zero-order delivery will be affected because of development of hydrostatic pressure within the core. This hydrostatic pressure may not be relieved because of the small orifice size and may lead to deformation of delivery system, thereby resulting in unpredictable drug delivery. On the other hand, size of delivery orifice should not also be too large otherwise; solute diffusion from the orifice may take place. There are mathematical calculations that can be used to calculate the optimum size of the delivery orifice. Drug release from osmotic pumps of nifedipine was studied as a function of orifice diameter and no significant differences were found in the release profiles for orifice diameter ranging from 0.25 to 1.41 mm.[39] Drug release was somewhat rapid with an orifice diameter of 2.0 mm possibly because of significant diffusion. On the other hand, a longer lag time and unpredictable and slower release rates were obtained from the systems without any orifice.

Membrane Types and Characteristics

To ensure that the coating is able to resist the pressure within the device, thickness of membrane is usually kept between 200 and 300 mm.[40] However, this may be problematic in cases where the drug is having low osmotic pressure because of which incomplete/ slow drug release may take place. Selecting membranes that are having high water permeabilities can be a solution to this problem. One approach that can be utilized is by using composite walls. The tablet cores are coated with a membrane that has a passageway through the wall for releasing the agent. The wall is formed of a multiplicity of materials comprising a material permeable to an external fluid and substantially impermeable to agent (like CA) and at least one additional material selected from a group of materials that imparts stability to the wall and enhances the permeability of the wall to fluids (like HPMC or hydroxyl butyl methylcellulose). Another approach that can be explored is to use a multilayer composite coating around the tablet.[41] The first layer is a thick microporous film that provides the strength required to withstand the internal pressure, while the second layer is a relatively thin SPM that produces the osmotic flux. Hence, high delivery rates can be obtained even for drugs with poor water solubility. Type, amount and nature of polymer, plasticizer and membrane thickness are important membrane variables in designing oral osmotic system.

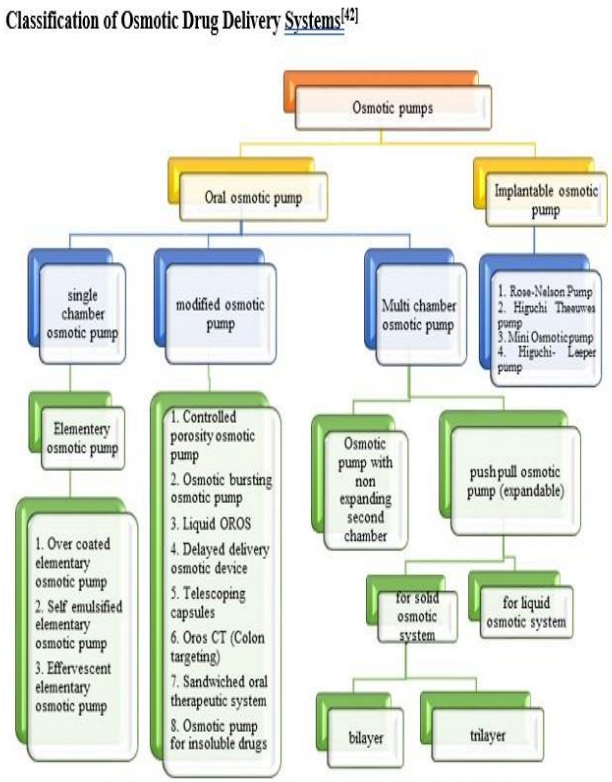

Figure 1: Classification of Osmotic Drug delivery System.

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Rose and Nelson the Australian scientists, were initiators of osmotic drug delivery.

Implantable Osmotic Pump

Rose and Nelson Pump 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 are comparable to modern push-pull osmotic pump. The major disadvantage of this pump is the water chamber, which must be charged before use of the pump.

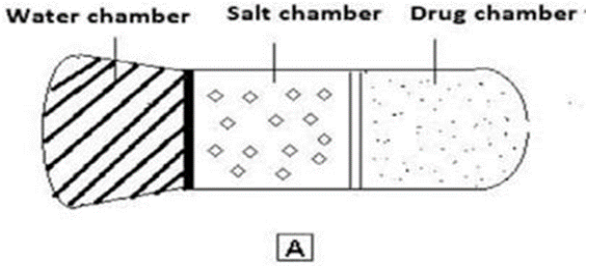

Figure 2: Rose and Nelson Pump

Higuchi-Leeper Pump

Figure 3 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. This pump consists of a rigid housing and semi-permeablemembrane supported on a perforated frame. It has a salt chamber containing a fluid solution with excess solid salt. Recent modification in Higuchi-Leeper pump also accommodates pulsatile drug delivery.

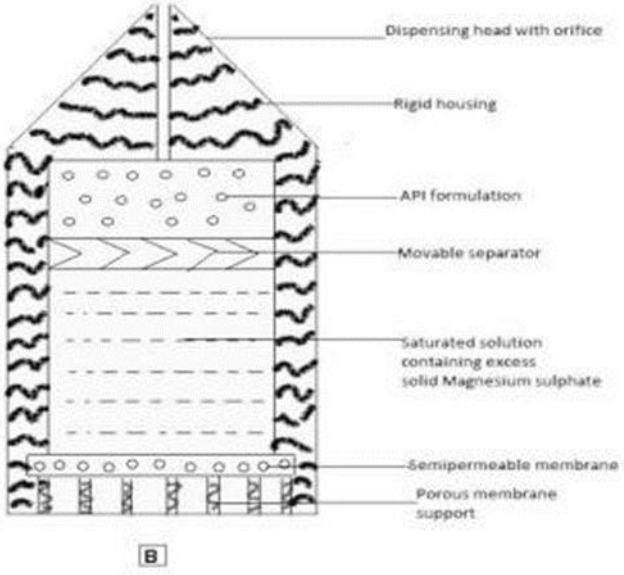

Figure 3: Higuchi-Leeper Pump.

Higuchi-Theeuwes Pump

Higuchi Theewus pump comprises a rigid rate controlling outer semi-permeable membrane surrounding a solid layer of salt coated on the inner side by an elastic diaphragm and on the outer side of the membrane. In use, water is osmotically drawn by the salt chamber, forcing drug from the drug chamber.

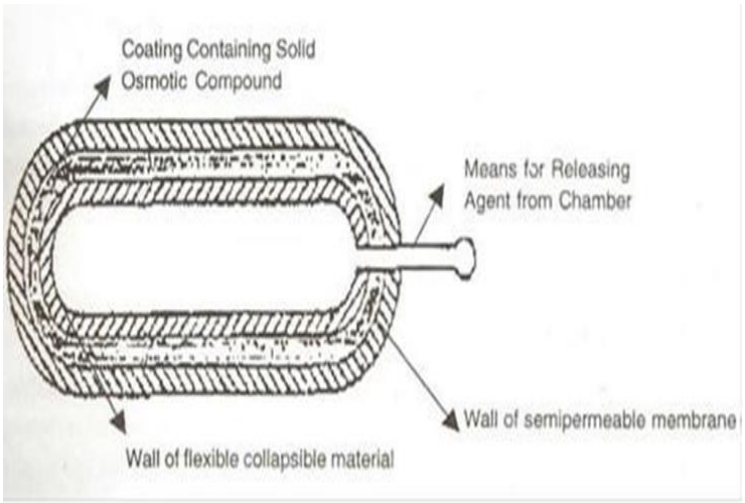

Figure 4: Higuchi-Theeuwes Pump.

Oral Osmotic Pumps
Single chamber osmotic pump (osmotic pump)

In this device, an active Elementary agent, having suitable osmotic pressure, is compressed in the form of a tablet, which is then coated with a semi-permeable material, and a small orifice is created in the membrane. When this tablet comes in contact with the aqueous environment of the GI tract, the agent inside the tablet draws water through the semi-permeable membrane because of the osmotic pressure gradient and forms a saturated solution inside the device. As the membrane is non-extensible, the increase in volume caused by the imbibition of water leads to the development of hydrostatic pressure inside the tablet. This osmotic imbibition of water result in formation of a saturated solution of drug within the core, 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, a lag time of 30-60 minutes is observed in most of the cases as the system hydrates before zero order delivery from the EOP begins. This system is suitable only for delivery of water soluble drugs.

Multiple chamber Osmotic pumps

Push-pull Osmotic Pump (PPOP)
The push pull system comprises of a bilayer or trilayer tablet core consisting of one push layer and one or more drug layers. The drug layer consists of poorly soluble drug, osmotic agents and suspending agents. The push layer contains other things, such as osmotic agents and water swellable polymers. A semi-permeable membrane surrounds the tablet core, as in the EOP system, and an orifice drilled into it on the drug layer side. These push pull osmotic pumps after coming in contact with the aqueous environment, polymeric osmotic layer swells and pushes the drug layer, and thus releases the drug in the form of fine dispersion or solution via the orifice at a constant zero order rate. Drug release kinetics from these systems has been hypothesized to be controlled by the hydration kinetics of both membrane and tablet core. Factors influencing drug delivery from PPOP was tested in two model drugs, Isradipine and chlorpheniramine which are respectively practically insoluble and freely soluble. Results revealed that regardless of drug properties, the release kinetics is mainly controlled by four factors i) plasticizer (PEG) proportion in the membrane ii) the tablet surface area iii) the osmotic agent proportion iv) the drug layer polymer grade.

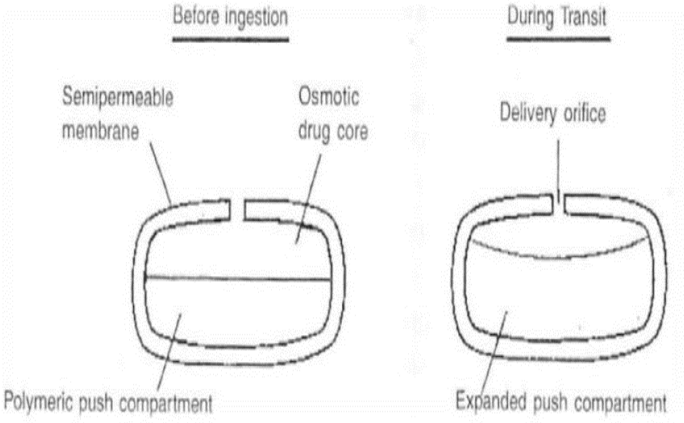

Figure 5: Push Pull Osmotic Pump tablet.

Osmotic Pump with Non Expanding Second Chamber
In such systems, second chamber is non-expanding in nature. But basing on the function of the second chamber such systems can be divided into two categories. In one category, the second chamber is used to dilute the drug solution before leaving the device. This is useful because in certain cases saturated solution of the drug may cause irritation of GI tract. The second category consists of two separate EOP tablets formed into a single tablet. The device releases both the drugs simultaneously.

Types of Osmotically Controlled Oral Drug Delivery

Sandwiched Osmotic Tablet System.
In sandwiched osmotic tablet (SOTS), a tablet core consisting of a middle push layer and two attached drug layers is coated with a SPM. Both the drug layers are connected to the outside environment via two delivery orifices (one on each side). After coming in contact with the aqueous environment, the middle push layer containing swelling agents swells and the drug is released from the delivery orifices. The advantage with this type of system is that the drug is released from the two orifices situated on two opposite sides of the tablet and thus can be advantageous in case of drugs which are prone to cause local irritation of gastric mucosa. Exempting side identification before drilling, it is easier to prepare the SOTS than the push- pull osmotic tablet system. For example, a sandwiched osmotic tablet core surrounded by a cellulose acetate membrane with two orifices on both side surfaces, has been successfully prepared with the purpose of delivering nifedipine. Also Chronic diseases such as hypertension, diabetes, asthma etc. are treated using multiple drug therapies, which are vulnerable to incidences of side effects, poor patient compliance and slow improvement of patients. The SOTS could deliver two drugs for extended period of time in order to reduce the problems associated with multidrug therapy.

Sandwiched osmotic tablet system was attempted for the delivery of nifedipine and metoprolol tartarate simultaneously using polyethylene oxide 6, 00,000 and 8, 00,000 g/mole as thickening agent of drug layer and the expandable hydrogel of push layer respectively. The optimal osmotic pump tablet was found to deliver both drugs at a rate approximately zero order up to 16 h independent of the osmotic pressure of the release media.[42]

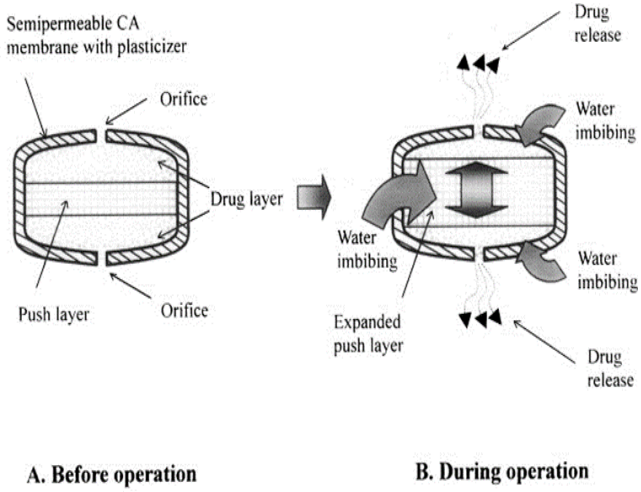

Figure 6: Sandwiched Osmotic Tablet.

Controlled Porosity Osmotic Pump (CPOP)

In such systems, the delivery orifice is formed by incorporation of water soluble ingredients in the coating material. Once the CPOP tablet comes in contact with the surrounding aqueous environment, water soluble additives dissolve resulting in an in situ formation of a microporous membrane. The resulting membrane substantially becomes permeable to both water and dissolved solutes and the mechanism of drug release was found to be setting up an osmotic gradient and thereby control the release of drugs.

Osmotic Bursting Pump

This device does not have an orifice in the outer membrane. This fact makes it less expensive because laser technology which drills the orifice in the outer membrane is not necessary. In osmotic bursting pumps, the penetration of water through the water insoluble membrane (e.g. Ethyl cellulose) hydrates the swelling agent (e.g. Hydroxy propyl methylcellulose). The expansion of swelling agent destroys the membrane, and subsequently leads to rapid drug release. The lag time for the drug release was precisely depends on the thickness of the outer membrane.

Liquid Oral Osmotic System (L-OROS)

Liquid OROS are designed to deliver drugs as liquid formulations and combine the benefits of extended release with high bioavailability.

Oral Osmotic System for Colon Targeting (OROS-CT)

OROS-CT is used as a once or twice a day formulation for targeted delivery of drugs to the colon. The OROS-CT can be a single osmotic agent or it can be comprised of as many as five to six push pull osmotic units 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, 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.

Osmotic Pump for Insoluble Drugs

The tablet core includes the drug, osmotic agent, wicking agent and solubility enhancers to dissolve the drug. Presence of the solubility enhancer in the core helps to dissolve the drug and the drug solution is delivered through the exit orifice to the GI lumen where it can be absorbed into the systemic circulation.

Monolithic Osmotic Tablet (MOT)

It constitutes a simple dispersion of water-soluble agent in polymer matrix. When the system comes in contact with the aqueous environment, water imbibition takes place rupturing the polymer matrix capsule surrounding the drug thus liberating it to the outside environment.

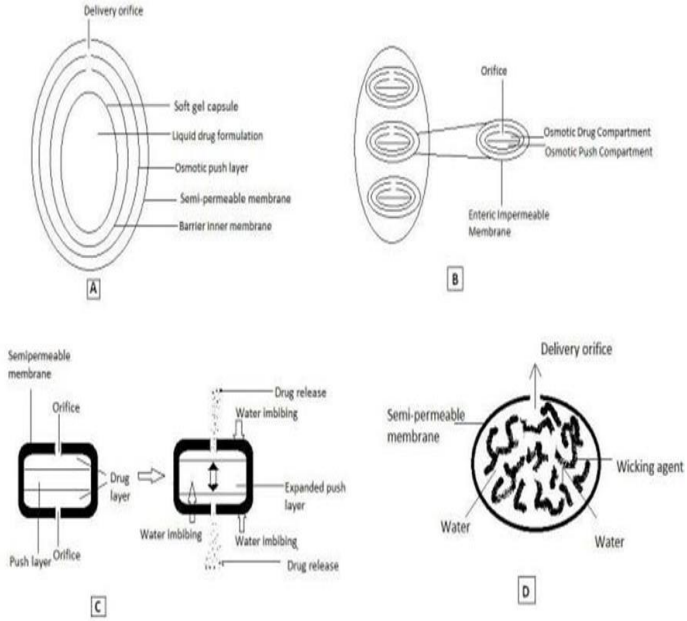

Figure 7: Specialized type of osmotic pumps.

A. Liquid oral osmotic system (L-OROS),
B. Oral osmotic system for colon targeting (OROSCT ®),
C. Sandwiched osmotic tablets,
D. Osmotic pump for insoluble drugs (Ensotrol®).

Table 2: Commercially Available Oros.[45]

Systems and introducers	Features of the system
ALZET	Miniature implantable osmotic pumps for laboratory animals. Different models having delivery rates from 0.25 to 10 µl/h and duration from1 day to 4 weeks available. Delivery profile independent of drug formulation.
OSMET	Used as experimental tools for human pharmacological studies and can be used for oral, rectal or vaginal administration. Available with release rate ranging from 8 to 120 µl/h.
Osmotic pumps for humans oral Elementary osmotic pump (Alza)	Single layer tablet for delivery of drugs having moderate water solubility. Can be utilized for zero order delivery as well as pulsed release.
Push-pull osmotic pump (Alza)	Bilayer tablet, used to deliver drugs having too low water solubility. Products such as Ditropan XL (Oxybutinin chloride), procardial XL and Glucotrol XL are based on this technology. Number of modifications available such as delayed push-pull, multi-layer push pull and push stick system.
L- OROS (Alza)	Designed to deliver lipophilic liquid formulations and is suitable for delivery of insoluble drugs
OROS-CT	For targeted drug delivery to colon and can be used for local or systemic delivery
Portab System (Andrx Pharma, USA)	Tablet core consists of soluble agent, which expands and creates microporous channels for drug release.
SCOT (Single Composition Osmotic Tablet) (Andrx Pharma, USA)	Utilizes various osmotic modulating agents and polymer coating to provide zero order release.
ENSOTROL drug delivery system (ShireLabs)	Utilizes various solubilizing and wicking agents for delivery of poorly soluble drugs.
Zero Os (ADD drug delivery technologies)	Specially for delivery of lipophilic compounds. Consists of gel forming agents in the core that form gel after coming in contact with water. Drug is released as a fine dispersion.
Implantable DUROS (Duract Corp.)	Miniature, implantable osmotic pumps for long term, parenteral, zero order delivery of patent therapeutic agents. Deliver drugs at a precisely controlled and constant rate within therapeutic range for long periods.

Advantages

- Easy to formulate, simple in operation, well characterized and understood. Improves patient compliance with reduced frequency.
- Prolonged therapeutic effect with uniform blood concentration. They typically give a zero order release profile after an initial lag and deliveries may be delayed or pulsed if desired.
- Drug release is independent of gastric pH and hydrodynamic condition and release mechanisms are not dependent on drug. The release from osmotic systems is minimally affected by the presence of food in gastrointestinal tract.
- A high degree of in-vitro and in-vivo correlation (IVIVC) is obtained in osmotic systems.
- The rationale for this approach is that the presence of water in gastrointestinal tract is relatively constant, at least in terms of the amount required for activation and controlling osmotically based technologies.
- Higher release rates are possible with osmotic systems compared with conventional diffusion-controlled drug delivery systems. The release rate of osmotic systems is highly predictable and can be programmed by modulating the release control parameters.

Disadvantages [23]

- Dose dumping, rapid development of tolerance and expensive.
- Retrieval therapy is not possible in the case of unexpected adverse events.
- If the coating process is not well controlled there is a risk of film defects, which results in dose dumping. Size hole is critical.
- Special equipment is required for making an orifice in the system.
- Residence time of the system in the body varies with the gastric motility and food intake.
- It may cause irritation or ulcer due to release of saturated solution of drug.

CONCLUSION

The objectives of to develop the osmotic drug delivery system is to reduce the frequency of dose administration and to improve the bioavailability of the drug and protect the drug from gastric environment. To maintain therapeutically effective plasma drug concentration levels for a longer duration thereby reducing the dosing frequency and to minimize the plasma drug concentration fluctuations at steady state by delivering drug in a controlled and a reproducible manner.

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