Review Article

An Overview on Osmotically Driven Systems

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ABSTRACT

The immediate release conventional dosage form lack in the efficiency of controlling the proper plasma drug concentration. This results in the development of various controlled drug delivery system. Among which the osmotic drug delivery system (ODDS) are gaining importance as these systems deliver the drug at specific time as per the path physiological need of the disease, resulting in improved patient therapeutic efficacy and compliance. They work on the principle of osmotic pressure for controlling the delivery of the drug. When these systems are exposed to water, low levels of water soluble additive is leached from polymeric material i.e. semi permeable membrane and drug releases in a controlled manner over an extended period of time. The release of the drug is independent of physiological factors of the GIT to a large extent. This review highlights the theoretical concept of osmotic drug delivery, principal, mechanism, types of osmotic drug delivery systems, factors affecting the drug delivery system, advantages and disadvantages of these delivery systems, formulation aspects, marketed status and the patents available on osmotic drug delivery system. Overall, osmotically driven systems appear to be a promising technology for product life-cycle strategies.

Keywords: Osmosis, Osmotic pressure, Osmotic drug delivery system, Semi permeable membrane.

INTRODUCTION

During the past three decades significant advances have been made in the area of novel drug delivery. The reason for this development is relatively low development cost and time required for introducing a NDDS ($20–50 million and 3–4 years, respectively) as compared to a new chemical entity (approximately $500 million and 10–12 years, respectively).[1] In the form of NDDS, an existing drug molecule can get a 'new life,' thereby, increasing its market value, competitiveness, and patent life. A number of design options are available to control or modulate the drug release from a dosage form. Majority of per oral dosage form fall in the category of matrix, reservoir or osmotic system. In matrix system, the drug is embedded in polymer matrix and the release takes place by partitioning of drug into the polymer matrix and the release medium. In contrast, reservoir systems have a drug core surrounded coated by the rate controlling membrane.[2] However factor like pH, presence of food and other physiological factor may affect drug release from conventional controlled release systems. Osmotic systems utilize the principle of osmotic pressure for the delivery of drugs. Drug release from these systems is independent of pH and other physiological parameter to a large extent and it is possible to modulate the release characteristic by optimizing the properties of drug and system. Oral osmotically driven systems have primarily evolved from being device concepts for the delivery of veterinary medicines, namely Rose-Nelson, Higuchi-Leeper and Higuchi-Theeuwes pumps.[3-5] Using osmotic pressure as the energy source, the semi permeable membrane controls water inflow, generating hydrodynamic pressure inside the device and, thereby controlling drug delivery. All these technologies have in common the 'semi permeable' membrane controlling the drug delivery rate. Alza corporation of the USA was first to develop an oral osmotic pump and today also they are the leaders in this field with a technology named OROS. Osmotic drug delivery has come long way since Australian pharmacologist Rose and Nelson developed an implantable osmotic pump in 1955. Next quantum leap in osmotic dosage form came in 1972 when Theuwes invented elementary osmotic pump. After that many of have been invented which enable controlled delivery of almost all drugs. The first two products indomethacin, Osmosin and phenylpropanolamine, AcutrimTM, were launched in the 1980s.[6,7] In contrast to the originally anticipated business success, Osmosin had to be withdrawn from the market due to severe side effects such as GI irritation and perforation of the intestinal wall. This opened a crucial debate on the safety of administering non-degradable systems such as OODS, the prolonged delivery of irritating drug substances from delivery systems that are somewhat hindered in their transit through the GI tract and thereby delivering the drug to one small region of the gut wall (i.e. area of the GI mucosa directly facing the delivery system orifice) over extended periods of time and the importance of adapting the drug delivery system to the drug properties and risks. Due to these adverse events seen with the OODS formulations of Indomethacin, a well-known anti-inflammatory drug since the 50s, 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 localized 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.[8,9] 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. 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, ConcertaTM, seemed to mark the end of the controversies concerning good treatment compliance with the technology and demonstrated tolerability in children.[10] The history of the OODS reflects the difficulty in developing an innovative technology in the pharmaceutical field. Often times, the return on the initial investment made to develop the technology was delayed after several setbacks during development. Currently, OODSs are becoming attractive technologies because of their abilities to enhance the clinical profile of certain therapeutic agents and to positively differentiate a drug product from others on the market. However, a systematic approach is needed in order to apply a coherent development strategy to future OODS products. The bioavailability of drug from these formulations may vary significantly, depending on factors such as physico-chemical properties of the drug, presence of excipient, various physiological factors such as the presence or absence of food, pH of the GI tract, GI motility, etc. To overcome this limitation of oral route is replied by parenteral route. This route offers the advantage of reduced dose, targeting of site and avoiding GI stability, hepatic by-pass of drug molecule.[11]

Principal and Mechanism of Osmotically Controlled Drug Delivery System [12,13]

The first report of an osmotic effect dates to Abbenollet {1748}. But Pfeffer obtained the first quantitative measurement in 1877. In Pfeffer experiment a membrane permeable to water but impermeable to sugar is used to separate a sugar solution from pure water. A flow of water then takes place into the sugar solution that cannot be halted until a pressure π is applied to the sugar solution. Pfeffer showed that this pressure, the osmotic pressure π of the sugar solution is directly proportional to the solution concentration and the absolute temperature. Within few years, Vant Hoff had shown the analogy between these results and ideal gas laws by the expression

$$\pi = Ø\ c\ RT$$

Where, p = Osmotic pressure, π = osmotic coefficient, c = molar concentration, R = gas constant T = Absolute temperature. Osmotic pressure is a colligative property, which depends on concentration of solute that contributes to osmotic pressure. Solutions of different concentrations having the same solute and solvent system exhibit an osmotic pressure proportional to their concentrations. Thus a constant osmotic pressure, and thereby a constant influx of water can be achieved by an osmotic delivery system that results in a constant zero order release rate of drug. Osmotic pressure for concentrated solution of soluble solutes commonly used in controlled release formulation are extremely high ranging from 30 atm for sodium phosphate up to 500 atm for a lactose-fructose mixture, as their osmotic pressure can produce high water flow across semi permeable membrane. The osmotic water flow through a membrane is given by the equation

$$dv\backslash dt = A\ Q\ \Delta\ \pi\backslash\ L$$

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

A in cm^2,

L = thickness,

Q = permeability

Δ π = the osmotic pressure difference between the two solutions on either side of the membrane.

This equation is applicable for the membrane permeable to water but completely impermeable to osmotic agent. The basic equation which applies to osmotic systems is

$$dM/dt = dV/dt\ x\ c \quad \text{.....(eq 1)}$$

Where, dM/dt= mass release,

dV/dt= volumetric pumping rate,

c = concentration of drug.

But, $dV/dt = (A/\ h)\ Lp\ (\sigma\ \Delta\pi\ -\Delta p)$

Where, A = membrane area,

h = thickness of membrane,

Lp= mechanical permeability,

σ = reflection coefficient,

Δπ = osmotic pressure difference,

Δp = hydrostatic pressure difference.

As the size of orifice delivery increases, Δp decrease,

so Δπ >> Δp and equation becomes

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

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

$$dV/dt = A/h\ Lp\ \sigma\pi = A/hk\ \pi$$

(k = Lpσ = membrane permeability)

Now, equation (1) can be given as

$dM/dt = (A/h)\, k\, \pi\, c = (A / h)\, k\, \pi\, S$

(S = solubility of drug, c taken as S)

Advantages of Osmotically Controlled Drug Delivery System[14,15]

1. They typically give a zero order release profile after an initial lag.
2. Deliveries may be delayed or pulsed if desired.
3. Drug release is independent of gastric pH and hydrodynamic condition.
4. They are well characterized and understood.
5. The release mechanisms are not dependent on drug.
6. A high degree of *in-vitro* and *in-vivo* correlation (ivivc) is obtained in osmotic systems.
7. The rationale for this approach is that the presence of water in git is relatively constant, at least in terms of the amount required for activation and controlling osmotically base technologies.
8. Higher release rates are possible with osmotic systems compared with conventional diffusion-controlled drug delivery systems.
9. The release from osmotic systems is minimally affected by the presence of food in gastrointestinal tract.
10. The release rate of osmotic systems is highly predictable and can be programmed by modulating the release control parameters.

Disadvantages of Osmotically Controlled Drug Delivery System

1. Expensive
2. If the coating process is not well controlled there is a risk of film defects, which results in dose dumping
3. Size hole is critical
4. Dose dumping
5. Retrival therapy is not possible in the case of unexpected adverse events.

Classification of Osmotically Controlled Drug Delivery System[16]

Many forms of osmotic pumps are reported in the literature but, in general they can be divided in oral and implantable systems.

1) Osmotic Implantable Formulation System

I. The Rose and Nelson Pump
II. Higuchi Leeper Pump
III. Higuchi Theuwes pump

2) Osmotic Oral Formulation System

I. Elementary Osmotic Pump (EOP)
II. Push Pull Osmotic Pump
III. Osmotic Bursting Osmotic Pump
IV. Liquid Oral Osmotic System
V. Sandwiched Osmotic Tablets (SOTS)
VI. Delayed Delivery Osmotic Device
VII. Monolithic Osmotic System
VIII. Controlled Porosity Osmotic Pump
IX. Telescopic Capsules
X. OROS-CT
XI. Osmat

IMPLANTABLE

Rose-Nelson Pump

Principle of the three-chamber Rose-Nelson osmotic pump first described in 1955. The forerunner of modern osmotic devices was the Rose-Nelson pump. Rose and Nelson were two Australian physiologists interested in the delivery of drugs to the gut of sheep and cattle. Their pump was never patented. The pump consisted of three chambers: a drug chamber, a salt chamber containing excess solid salt, and a water chamber. The drug and water chambers are separated by a 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 pumping rate of the Rose-Nelson pump is given by the Equation

$$dM/dT = dV/dT .C$$

Where dM/dt is the drug release rate, dV/dt is the volume flow of water into the salt chamber, and c is the concentration of drug in the drug chamber.

Higuchi-Leeper Pump

The Higuchi-Leeper pump was modified series of Rose-Nelson pump. It has no water chamber, and the device is activated by water imbibed from the surrounding environment. This means the pump can be prepared loaded with drug and then stored for weeks or months prior to use. The pump is activated when it is swallowed or implanted in the body. Higuchi-Leeper pumps contain a rigid housing, and the semi permeable membrane is supported on a perforated frame. This type of pump usually has a salt chamber containing a fluid solution with excess solid salt. Most recent system in this series used for pulsatile drug delivery system.

Higuchi-Theeuwes Pump

In the early 1970s, Higuchi and Theeuwes developed another, even simpler variant of the Rose-Nelson pump. As with the Higuchi-Leeper pump, water to activate the osmotic action of the pump is obtained from the surrounding environment. In the Higuchi-Theeuwes device, however, the rigid housing is dispensed with and the membrane acts as the outer casing of the pump. This membrane is quite sturdy and is strong enough to withstand the pumping pressure developed inside the device. The device is loaded with the desired drug prior to use. When the device is placed in an aqueous environment, release of the drug follows a time course set by the salt used in the salt chamber and the permeability of the outer membrane casing. Most of the Higuchi-Theeuwes pumps use a dispersion of solid salt in a suitable carrier for the salt chamber of the device as shown in figure 1.

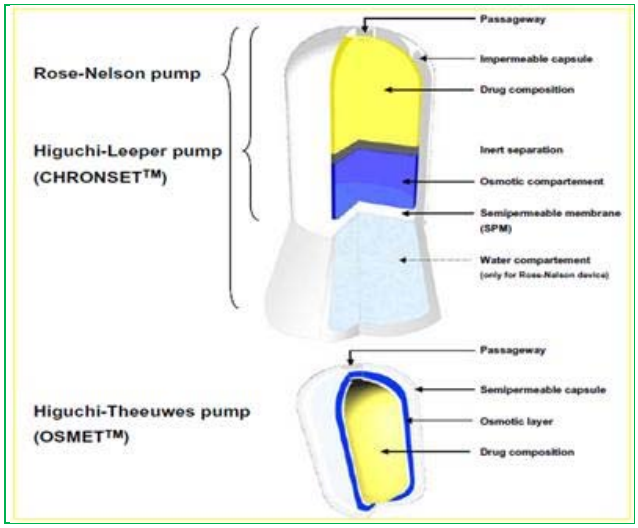

Figure 1: Schematic diagram of Osmotic Implantable System

More recently, osmotic principles have been applied to human parenteral therapy, resulting in the development of the DUROS® technology.[17] These technologies allow drug delivery for site-specific as well as systemic use for delivery periods of days to 1 year. All materials in the DUROS system were chosen for their biocompatibility and suitability for implant use. The drug-contacting materials are also screened for compatibility with the drug and the specific drug formulation excipients. Radiation sterilization (gamma) may be utilized to sterilize the final drug product. If the drug formulation cannot withstand sterilizing doses of radiation, then a DUROS subassembly is radiation sterilized, and the drug formulation is added in a final aseptic operation. Hence, the materials in the DUROS system were also screened for their ability to withstand sterilizing doses of radiation. DUROS® has the potential to provide more flexibility than competitive products regarding the types of drugs that can be administered, including proteins, peptides and genes because the drug dispensing mechanism is independent from the drug substance. ALZET osmotic pumps are miniature, implantable pumps used for research in mice, rats, and other laboratory animals. ALZET pumps operate by osmotic displacement. An empty reservoir within the core of the pump is filled with the drug or hormone solution to be delivered. Due to the presence of a high concentration of salt in a chamber surrounding the reservoir (but isolated from it by an impermeable layer), water enters the pump through its outer surface (a semi permeable layer). The entry of water increases the volume in the salt chamber, causing compression of the flexible reservoir and delivery of the drug solution into the animal via the exit port. ALZET pumps can be used for systemic administration when implanted subcutaneously or intraperitoneally. They can be attached to a catheter for intravenous, intracerebral, or intra-arterial infusion. ALZET pumps can also be used for targeted delivery, where the effects of a drug or test agent are localized in a particular tissue or organ, by means of a catheter. The pumps have been used to target delivery to a wide variety of sites including the spinal cord, spleen, liver, organ or tissue transplants, and wound healing sites. ALZET pumps have been used successfully to deliver hundreds of different compounds, including antibodies, chemotherapeutic drugs, cytokines, growth factors, hormones, and peptides.[18]

ORAL OSMOTIC PUMP

Elementary Osmotic Pump

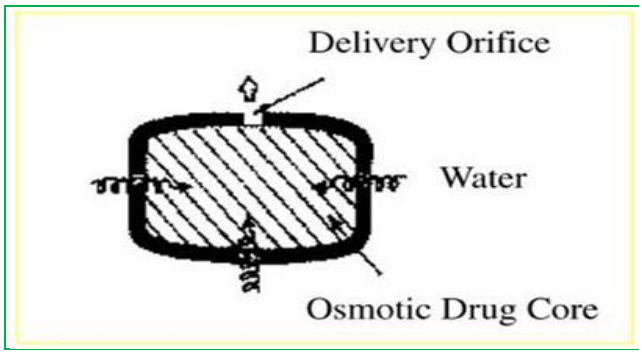

Figure 2: Schematic diagram of an Elementary Osmotic Pump

The seminal invention that made osmotic delivery a major method of achieving controlled drug release was that of the elementary osmotic pump by Theeuwes in 1974. The device is a further simplification of the Higuchi-Theeuwes pump, and eliminates the separate salt chamber by using the drug itself as the osmotic agent. 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. The elementary osmotic pump is a new delivery system for drugs. It delivers the agent by an osmotic process at a controlled rate[19]. Control resides in the: Water permeation characteristics of a semi permeable membrane surrounding the formulating agent as shown in figure number 2. Osmotic properties of the formulation Though 60-80 percent of drug is released at a

constant rate from the 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 system are suitable or delivery of drugs having moderate water solubility.

Push Pull Osmotic Pump

Push-pull osmotic systems (PPOS), also known as push-pull osmotic pumps, have been successfully developed and marketed to extend the release of poorly soluble compounds for various indications, such as hypertension, diabetes, and asthma. In these chronic disease treatments, PPOS were reported as a drug delivery technology reducing the food interaction often observed with poorly soluble drug substances as well as enabling a once-a-day administration and thereby patient compliance. Push Pull Osmotic Pump is possible to deliver both poorly water-soluble and highly water soluble drugs at a constant rate.[20] One layer (depict as the upper layer) contains drug in a formulation of polymeric, osmotic agent and other tablet excipients. This polymeric osmotic agent has the ability to form a suspension of drug in situ. When this tablet later imbibes water, the other layer contains osmotic and colouring agents, polymer and tablet excipients. These layers are formed and bonded together by tablet compression to form a single bilayer core. The tablet core is then coated with semi permeable membrane. After the coating has been applied, a small hole is drilled through the membrane by a laser or mechanical drill on the drug layer side of the tablet. When the system is placed in aqueous environment water is attracted into the tablet by an osmotic agent in both the layers as shown in figure number 3. The osmotic attraction in the drug layer pulls water into the compartment to form in situ a suspension of drug. The osmotic agent in the non-drug layer simultaneously attract water into that compartment, causing it to expand volumetrically and the expansion of non drug layer pushes the drug suspension out of the delivery orifice.

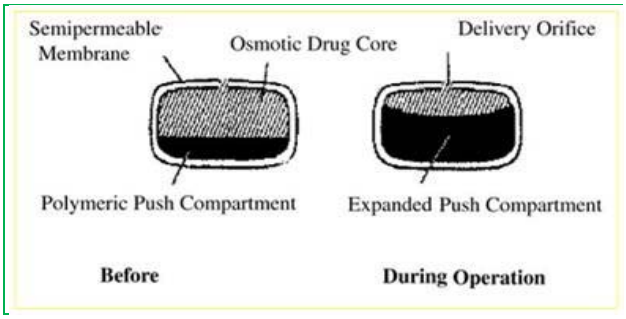

Figure 3: Schematic diagram of Push Pull Osmotic Pump

Osmotic Brusting Osmotic Pump

In this system delivery orifice is absent and size may be smaller. When it is placed in an aqueous environment, water is imbibed and hydraulic pressure is built up inside until the wall rupture and the content are released to the environment.[21] Varying the thickness as well as the area the semi permeable membrane can control release of drug. This system is useful to provide pulsated release.

Liquid Oral Osmotic System

Liquid OROS are designed to deliver drugs as liquid formulations and combine the benefits of extended release with high bioavailability. 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 semi permeable membrane coating. When the system is in contact with the aqueous environment water permeates across the rate controlling membrane and activate the osmotic layer. The expansion of the osmotic layer results in the development of hydrostatic pressure inside the system, thereby forcing the liquid formulation to be delivered from the delivery orifice. Whereas L OROS hardcap or softcap systems are designed to provide continuous drug delivery, the L OROS delayed liquid bolus drug delivery system is designed to deliver a pulse of liquid drug[22]. The delayed liquid bolus delivery system comprises three layers: a placebo delay layer, a liquid drug layer and an osmotic engine, all surrounded by rate controlling semi permeable membrane. The delivery orifice is drilled on the placebo layer end of the capsule shaped device. When the osmotic engine is expands, the placebo is released first, delaying release of the drug layer. Drug release can be delayed from I to 10 hour, depending on the permeability of the rate controlling membrane and thickness of the placebo layer.

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 agents swells and the drug is released from the two orifices situated on opposite sides of the tablet as shown in figure number 4 and thus SOTS can be suitable for drugs prone to cause local irritation of the gastric mucosa.[23]

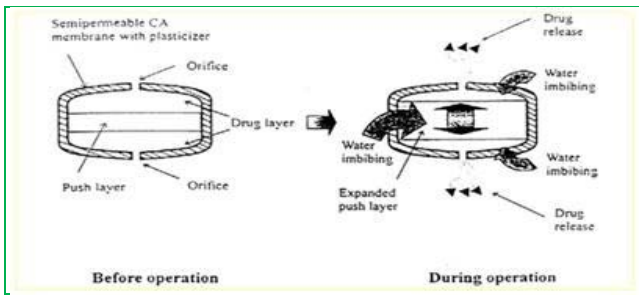

Figure 4: Schematic diagram of Sandwiched Osmotic Tablets

Delayed Delivery Osmotic Device

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 section. To assemble the delivery device, the desired active agent is placed into one of the sections by manual or automated fill mechanism. The bilayer tablet with the osmotic engine is placed into a completed cap part of the capsule with the convex osmotic layer pointed in to the closed end of the cap and the barrier into the closed end of the cap and the barrier layer exposed towards the cap opening. The open end of the filled vessel is fitted inside the open end of the cap, and the two pieces are compressed together until the cap, osmotic bilayer tablet and vessel fit together tightly. As fluid is imbibed the housing of the dispensing device, the osmotic engine expand and exerts pressure on the slidable connected first and second wall sections. During the delay period the volume of reservoir containing the active agent is kept constant, therefore a negligible pressure gradient exists between the environment of use and interior of the reservoir. As a result, the net flow of environmental fluid driven by the pressure enter the reservoir is minimal and consequently no agent is delivered for the period.[24]

Monolithic Osmotic System

It constitutes a simple dispersion of water-soluble agent in polymer matrix. When the system comes in contact in with the aqueous environment. Water imbibtion 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 then matrix in a serial fashion. However this system fails if more then 20 –30 volumes per liter of the active agents are incorporated in to the device as above this level, significant contribution from the simple leaching of the substance take place.

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 [25]. 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. 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, leading to the robust performance allude to above. The rate of flow dv/dt of water into the device can be represented as

$$dv / dt = Ak / h (Dp-DR)$$

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

Advantages of controlled porosity osmotic pumps

1. The OPT can be so designed that delivery of its drug would follow zero order kinetics and thus better control over the drug's *in-vivo* performance is possible.
2. The drug release from the osmotically controlled drug delivery systems are independent of the gastric pH and hydrodynamic conditions, which is mainly attributed to the unique properties of the SPM employed in the coating of osmotic formulations.
3. The delivery rate of drug from these systems is highly predictable and can be programmed by modulating the terms
4. Better release rates than those obtain with conventional diffusion based drug delivery systems.
5. Drug release from the OCODDSs exhibits significant *in vitro-in vivo* correlation [*ivivc*] within specific limits.

Disadvantages of controlled porosity osmotic pumps

1. Drug release from the osmotic system is affected to some extent by the presence of food.
2. Retrieval of therapy is not possible in the case of unexpected adverse events.

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 section. To assemble the delivery device, the desired active agent is placed into one of the sections by manual or automated fill mechanism. The bilayer tablet with the osmotic engine is placed into a completed cap part of the capsule with the convex osmotic layer pointed in to the closed end of the cap and the barrier into the closed end of the cap and the barrier layer exposed towards the cap opening. The open end of the filled vessel is fitted inside the open end of the cap, and the two pieces are compressed together until the cap, osmotic bilayer tablet and vessel fit together tightly. As fluid is imbibed the housing of the dispensing device, the osmotic engine expand and exerts pressure on the slidable connected first and second wall sections. During the delay period the volume of reservoir containing the active agent is kept constant, therefore a negligible pressure gradient exists between the environment of use and interior of the

reservoir. As a result, the net flow of environmental fluid driven by the pressure enter the reservoir is minimal and consequently no agent is delivered for the period.

Oros-CT

OROS-CT is used as a once or twice a day formulation for targeted delivery of drugs to the colon. The OROS-CT can be a single osmotic agent or it can be comprised of as many as five to six push pull osmotic unit filled in a hard gelatin capsule. After coming in contact with the gastric fluids, gelatin capsule dissolved and the enteric coating prevents entry of fluids from stomach to the system as the system enters into the small intestine the enteric coating dissolves and water is imbibed into the core thereby causing the push compartment to swell. At the same time flowable gel is formed in the drug compartment, which is pushed out of the orifice at a rate, which is precisely controlled, by the rate of water transport across the semi permeable membrane[26].

Osmat

It is a novel osmotically driven matrix system, which utilizes the hydrophilic polymers to swell, and gel in aqueous medium forming a semi permeable membrane in-situ releases from such a matrix system containing an osmogen could, therefore be modulated by the osmotic phenomenon. Osmat thus judiciously combines both matrix osmotic characteristics resulting in a quantum improvement in drug delivery from swellable matrix system. Osmat produces controlled drug release with adequate delivery rates in an agitation in dependent manner. Thus osmat represents simple, versatile, and easy to fabricate osmotically driven controlled drug delivery system based upon low cot technology[27].

Formulation of Osmotically Controlled Drug Delivery System[28]

1. Drug
2. Osmotic agent
3. Semi permeable membrane
4. Plasticizers

1) **Drugs**

Ideal characteristics of drug candidate for osmotically controlled drug delivery

1. Short biological half-life (2-6h)
2. Highly potent drug
3. Required for prolonged treatment e.g. Nifedipine, Glipizide, Virapamil.

2) **Osmotic agents**

Osmogents used for fabrication of osmotic dispensing device are inorganic or organic in nature a water soluble drug by itself can serve the purpose of an osmogent.

a) **Inorganic water-soluble osmogents**

Magnesium sulphate, Sodium chloride, Sodium sulphate, Potassium chloride, Sodium bicarbonate.

b) **Organic polymer osmogents**

Sodium carboxymethyl cellulose**,** Hydroxypropylmethyl cellulose**,** Hydroxyethylmethylcellulose**,** Methylcellulose**,** Polyethylene oxide**,** polyvinyl pyrollidine.

3) **Semi Permeable Membrane**

The semi permeable membrane should be a stable both to the outer inner environment of the device. The membrane must be sufficiently rigid so as to retain its dimensional integrity during the operational lifetime of the device. The membrane should also be relatively impermeable to the contents of dispenser so that osmogent is not lost by diffusion across the membrane finally, the membrane must be biocompatible.

Ideal Property of Semi Permeable Membrane

a. The material must possess sufficient wet strength (-105) and wet modulus so as to retain its dimensional integrity during the operational lifetime of the device.

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

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

d. The membrane should also be biocompatible.

e. Rigid and non-swelling.

f. Should be sufficient thick to withstand the pressure within the device.

4) **Plasticizers**

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

a. Polyethylene glycols

b. Ethylene glycol monoacetate; and diacetate- for low permeability

c. Tri ethyl citrate

d. Diethyl tartarate or Diacetin- for more permeable films

Factors Affecting Drug Release Rate

1. Drug Solubility

2. Osmotic Pressure
3. Delivery Orifice
4. Coating Membrane

Drug Solubility

APIs for osmotic delivery should have water solubility in the desired range to get optimize drug release. However, by modulating the solubility of these drugs within the core, effective release patterns may be obtained for the drugs, which might otherwise appear to be poor candidate for osmotic delivery.

Solubility-modifying approaches

- Use of swellable polymers: vinyl acetate copolymer, polyethylene oxide have uniform swelling rate which causes drug release at constant rate.
- Use of wicking agents: These agents may enhance the surface area of drug with the incoming aqueous fluids. e.g. colloidal silicon dioxide, sodium lauryl sulfate, etc. Ensotrol® technology uses the same principle to deliver drugs via osmotic mechanism.
- Use of effervescent mixture: Mixture of citric acid and sodium bicarbonate which creates pressures in the osmotic system and ultimately controls the release rate.
- Use of cyclodextrin derivatives: They are known to increase solubility of poorly soluble drugs. The same phenomenon can also be used for the osmotic systems.
- Use of alternative salt form: Change in salt form of may change solubility.
- Use of encapsulated excipients: Solubility modifier excipient used in form of mini-tablet coated with rate controlling membrane.
- Resin Modulation approach: Ion-exchange resin methods are commonly used to modify the solubility of APIs. Some of the resins used in osmotic systems are Poly (4-vinyl pyridine), Pentaerythritol, citric and adipic acids.
- Use of crystal habit modifiers: Different crystal form of the drug may have different solubility, so the excipient which may change crystal habit of the drug can be used to modulate solubility.
- Co-compression of drug with excipients: Different excipients can be used to modulate the solubility of APIs with different mechanisms like saturation solubility, pH dependent solubility. Examples of such excipients are organic acids, buffering agent, etc.

Osmotic pressure

The next release-controlling factor that must be optimized is the osmotic pressure gradient between inside the compartment and the external environment. The simplest and most predictable way to achieve a constant osmotic pressure is to maintain a saturated solution of osmotic agent in the compartment.

Size of delivery orifice

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 build up in the system. The typical orifice size in osmotic pumps ranges from 600µ to 1 mm. 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, CO_2 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 semi permeable coating: e.g. controlled porosity osmotic pump.

Coating Membrane

Thickness of the membrane has a profound effect on the drug release from osmotic systems. The release rate from osmotic systems is inversely proportional to membrane thickness. The thickness can be controlled by altering the permeability of coating polymer with different pharmaceutical plasticizer such as PEG-200, PEG-600, dibutyl sebacate, triethyl phosphate, diethyl tartrate, diacetin and ethylene glycol.

Evaluation Parameter of Osmotic Drug Delivery Formulation

- Characterization of dosage form
- Effect of osmotic agents
- Swelling properties
- Membrane stability and thickness
- Orifice diameter and drug release
- In-vitro drug release study

Marketed Products[29]

The products developed and marketed based on OODS technology cover primarily four therapeutic areas: cardiovascular (35%), neurological (25%), seasonal (25%) and metabolic disorders (15%) as given in table number 1. These products have been mainly developed by two

companies, the former Alza Corp., which was later acquired by Johnson & Johnson and is the historical inventor of the technologies, with 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. The increasing number of marketed products has translated into a twofold increase in the OODS revenues in the past 5 years, reaching about 3 billion dollars worldwide annual sales.

Table 1: Marketed Osmatically Driven System

Marketed Product	Active Pharmaceutical Ingredient	Design	Dose (mg)
Cardiovascular Disorders			
UT-15C	Treprostinil diethanolamine	SEOP	1
LCP-Lerc	Lercanidipine	DOEOP	20
Cardura CR	Doxazosin mesylate	PPOP	4–8
Concerta	Methylphenidate HCl	PSOP	18–54
Ditropan XL Ditropan UD/ Tavor	Oxybutynin chloride	PPOP, SEOP	5–15
Teczem	Enalapril Diltiazem	CPOP	280
Tiamate Dilacor XR	Diltiazem HCl	CPOP, SCOT	120–240
Covera HS	Verapamil HCl	COER	180–240
DynaCirc CR	Isradipine	PPOP	5–10
Minipress XL or Alpress LP	Prazosin	PPOP	2.5–5
Procardia XL/Adalat CC Nifed Sol	Nifedipine	PPOP, DOEOP	30–90
Metabolic disorders			
Topamax	Topiramate	PSOP	25–175
AltoPlus XR	Metformin HCl, Pioglitazone HCl	SCOT	500–850
Fortamet	Metformin HCl	SCOT	500–1000
Altoprev	Lovastatin	EOP	10–60
Glucotrol XL	Glipizide	PPOP	2.5–10
Nervous and neuronal disorders			
Flexeril XL	Cyclobenzaprine	EOP	15–30
Oxycontin	Oxycodone	PPOP	10
Jusnista	Hydromorphone	PPOP	8–64
Invega	Paliperidone	PPOP	3–12
Elafax XR	Venlafaxine HCl	EOP	37.5–150
Tegretol XL	Carbamazepine	SEOP	100–400
Osmosin	Indomethacin	EOP	75
Respiratory and Seasonal disorders			
Teosona Sol	Theophylline	DOEOP	400
Allegra D 24 h	Pseudoephedrine HCl	DOEOP	240
Loremex	Pseudoephedrine HCl	DOEOP	240
Mildugen D	Pseudoephedrine HCl	DOEOP	240
Efidac 24 brompheniramine	Pseudoephedrine HCl	EOP	240
Efidac 24 chlorpheniramine	Pseudoephedrine HCl	EOP	240
Efidac 24 Sudafed 24h	Pseudoephedrine HCl	EOP, DOEOP	240
Volmax	Albuterol	EOP	4–8
Acutrim	Phenyl propanolamine	DOEOP	75
Gastrointestinal disorders			
Osmoran 300	Ranitidine HCl	DOEOP	300

Patents On Osmotic Drug Delivery System [30,31]

Some of the patents available on osmotic drug delivery system are listed in table number 2 and 3 as follows;

Table 2: Patents of Drug Formulation in the Form of Elementary Osmotic Pump

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

CONCLUSION

Development efforts of oral osmotically driven systems (OODSs) during recent years have been very dynamic with the emergence of new technologies and products. It has been recognized as an attractive niche for the pharmaceutical and health industry. Among various NDDS, osmotic pumps have matured from their use with laboratory animals to the most reliable controlled release

systems for human. Osmotically controlled drug delivery system use osmotic pressure for controlled delivery of active agents. The clinical benefits of OODS mainly reside in their capacity to deliver a drug at a pre-determined rate, independent of physiological parameters such as food intake or patient age. Because of their unique advantages over other types of dosage forms, osmotic pumps from a class of their own among the various drug delivery technologies, and a variety of products based on this technology are available on the market. Despite the controversy concerning the safety in the administration of non-disintegrable tablets, the reported clinical benefits have opened up new perspectives to the future development of drugs as oral osmotically driven systems.

Table 3: Patent of Drug Formulation in the Form of Multi Chamber Osmotic Pump

Year	U.S. Patent No.	Drug
1986	4612008	Diclofenac sodium
1988	4765989	Nifedipine and α blocker
1988	4783337	Calcium antagonist, ACE inhibitor
1989	4812263	Isadipine
1989	4837111	Doxazocin
1989	4859470	Diltiazem
1990	4904474	Beclomethasone
1990	4948593	Contraceptive Steroid
1991	5024843	Glpizide
1991	5028434	Nivadipine
1992	5160744	Verapamil
1992	5091190	Glipizide
1993	5185158	Tandospirone
1993	5192550	Antiparkinsons drug
1993	5248310	Beclomethasone(oral)
1996	5545413	Glipizide
1997	5591454	Glipizide
2003	20030224051	Oxycodone
2004	20040091529	Topiramine
2005	20050232995	Resperidone and Paliperidone

REFERENCES

1. Verma RK, Garg S, Current status of drug delivery technologies and future directions, Pharm. Technol.-On Line (http: / /www.pharmaportal.com), 25, 2001, 1–14.
2. Verma RK, Mishra B, Garg S, Osmotically controlled oral drug delivery, Drug Dev Ind Pharm., 26(7), 2000, 695-708.
3. Rose S, Nelson JF, A continuous long-term injector, Aust. J. Exp. Biol., 33, 1955, 415.
4. Higuchi T, Leeper H, Alza Corp. Osmotic dispenser, US Patent 3732, 1973, 865.
5. Theeuwes F, Higuchi T, Osmotic dispensing device for releasing beneficial agent, US Patent 3845, 1974 ,770.
6. Theeuwes F, Swanson D, Wong P, Bonsen P, Place V, Heimlich K, Kwan KC, Elementary osmotic pump for indomethacin, J. Pharm. Sci., 72 (3,) 1983, 253–258.
7. Weintraub M, Ginsberg G, Stein EC, Sundaresan PR, Schuster B, Connor PO, Byrne LM, Phenyl propanolamine OROS (Acutrim) vs. placebo in combination with caloric restriction and physician-managed behavior modification, Clin. Pharmacol. Ther., 39 (5), 1986, 501–509.
8. Weintraub M, Horn JH, Krakoff L, Vetrovec G, committee review of nifedipine gits – new modality for angina and hypertension, Hosp. Form., 25, 1990, 10–14.
9. Ruilope LM, Long-term protection in at-risk hypertensive patients – a role for nifedipine GITS, Blood Press, 11(2), 2002, 106–109.
10. Coghill D, Seth S, Osmotic controlled-release methylphenidate for the treatment of ADHD, Expert Opin. Pharmacother., 7 (15), 2006, 2119–2138.
11. Bhatt PP, Osmotic drug delivery systems for poorly water soluble drugs, Pharmaventures Ltd., Oxford, UK, 2004, 26-29.
12. Pfefer, W E P; Osmotishe Umtersuchen, Leipzig., 1877, 232.
13. Li X, Jasti BR, Osmotic controlled drug delivery systems, In: Design of controlled release of drug delivery systems, McGraw Hill, 2006, 203-229.
14. Fix J, In: Encyclopedia of controlled drug delivery, Edmathiowitz, vol-2, John Wiley and sons, Inc 700.
15. Kaushal AM, Garg S, An update on osmotic drug delivery patents, Pharm Tech., 2003, 38-44.
16. Thakor RS, Majmudar FD, Patel JK, Rajaput GC, Review: Osmotic drug delivery systems current scenario Journal of Pharmacy Research 3 (4), 2010, 771-775.
17. Zentner GM, Himmelstein KJ, Rork GS, Multiparticulate controlled porosity osmotic, US Patent 4851228, 1989.
18. Baker RW, Controlled release delivery system by an osmotic bursting mechanism, US Patent 3952741, 1976.
19. Theeuwes F, Elementary Osmotic Pump. J Pharm Sci, 64, 1975, 1987-1991.
20. Parmar NS, Vyas SK, Jain NK, In: Advanced in controlled and novel drug delivery, CBS publisher, 22-25.
21. Theuwes F, Wong P, Burkoth TL, Fox DA, Bicek PR, colonic drug absorption and metabolism, Marcel Decke, new york, 1993, 137-158.
22. Zentner M, Gerald, Himmerstein SJ, The Controlled Porosity Osmotic Pump, J Control Rel., 1, 1985, 269-282.
23. Zentner M, Rork GS, Himmelstein KJ, Osmotic flow through controlled porosity films: An approach to delivery of water soluble compounds, J Control Release, 2, 1985, 217-229.
24. Jerzewski R and Chien Y, Osmotic drug delivery. In: Treatise on controlled drug delivery: Fundamentals, optimization, Application. Marcel Dekker, 1992, 225-253.
25. Liu L, Khang G, Lee B, Rhee JM, Nifedipine controlled delivery by sandwiched osmotic tablet system, J Control Release, 68, 2000, 145-156.

26. Gaebler F, Laser drilling enables advanced drug delivery systems, Coherent article for Pharmaceutical Manufacturing, 2007, 1-7.
27. Wong P, Barclay B, Deters JC, Theeuwes F, Osmotic device with dual thermodynamic activity, US Patent 4612008, 1986.
28. Verma RK, Krishna D, Garg S, Review on Formulation aspects in the development of osmotically controlled oral drug delivery systems Journal of Controlled Release, 79, 2002, 7–27.
29. Verma RK, Arora S, Garg S, Osmotic pumps in drug delivery, Crit Rev. Ther. Drug Carrier Syst., 21(6), 2004, 477–520.
30. Ghosh T, Ghosh A, Drug Delivery through Osmotic Systems – An Overview, Journal of Applied Pharmaceutical Science 01(02), 2011, 38-49.
31. www.uspto.gov.in.

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