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Review Article

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OSMOTIC PUMPS: A REVIEW

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ABSTRACT

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

Keywords: Osmosis, osmotic pressure, osmogen, semi permeable membrane.

INTRODUCTION

During the past three decades significant advances have been made in the area of novel drug delivery. This was in part due to the evolving discipline of biopharmaceutics, pharmacokinetics and pharmacodynamics. In a typical therapeutic regimen the drug dose and dosing interval are optimized to maintain drug concentration within the therapeutic window, thus ensuring efficacy while minimizing toxic effects. Survey indicated that dosing more than one or twice daily, greatly reduces patient compliance. So in recent year considerable attention has been focused on the development of novel drug delivery system and the main reason for this paradigm shift is relatively low development cost and time required for introducing a novel drug delivery system as compared to a new chemical entity. In the form of novel drug delivery system, an existing drug molecule can get a new life there by increasing its market value competitiveness and patent life among the various novel drug delivery system available in the market, per oral controlled release system hold the major market share because of their obvious advantages of ease of administration and better patient compliance. These products provide significant benefits over immediate release formulation, including greater effectiveness in the treatment of chronic conditions, reduced side effects, and greater patient convenience due to simplified dosing schedule.[1]

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. 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.[2] The oral osmotic pumps have certainly came a long way and the available products on this technology and number of patent granted in the last few years makes it presence felt in the market.[3] They are also known as gastro intestinal therapeutic system. 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.[4]

The bioavailability of drug from these formulations may vary significantly, depending on factors such as physico-chemical properties of the drug, presence of excipient,

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various physiological factors such as the presence or absence of food, pH of the GI tract, GI motility, etc.[5] 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.

In the recent years, pharmaceutical research has led to the development of several novel drug delivery systems. The role of drug development is to take a therapeutically effective molecule with sub-optimal physicochemical and/or physiological properties and develop an optimized product that will still be therapeutically effective but with additional benefits such as[6]

- Greater effectiveness in the treatment of chronic conditions,
- Sustained and consistent blood levels within the therapeutic window,
- Enhanced bioavailability,
- Reduced interpatient variability,
- Customized delivery profiles,
- Decreased dosing frequency,
- Improved patient compliance due to simplified dosing schedule,
- Reduced side effects.

Osmosis

Osmosis refers to the process of movement of solvent molecules from lower concentration to higher concentration across a semi permeable membrane. Osmosis is the phenomenon that makes controlled drug delivery a reality. Osmotic pressure created due to imbibitions of fluid from external environment into the dosage form regulates the delivery of drug from osmotic device. Rate of drug delivery from osmotic pump is directly proportional to the osmotic pressure developed due to imbibitions of fluids by osmogen. Osmotic pressure is a colligative property of a solution in which the magnitude of osmotic pressure of the solution is independent on the number of discrete entities of solute present in the solution. Hence the release rate of drugs from osmotic dispensing devices is dependent on the solubility and molecular weight and activity coefficient of the solute (osmogent).

Principles of Osmosis[7,8]

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.[9] 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 and Δ π = the osmotic pressure difference between the two solutions on either side of the membrane. This equation is strictly for completely perm selective membrane that is membrane permeable to water but completely impermeable to osmotic agent.

Osmotically controlled drug delivery systems

Osmotic pressure is used as driving force for these systems to release the drug in controlled manner. Osmotic drug delivery technique is the most interesting and widely acceptable among all other technologies used for the same. Intensive research has been carried out on osmotic systems and several patents are also published. Development of osmotic drug delivery systems was pioneered by Alza and it holds major number of the patents analyzed and also markets several products based on osmotic principle. These systems can be used for both route of administration i.e. oral and parenterals. Oral osmotic systems are known as gastro-intestinal therapeutic systems (GITS). Parenteral osmotic drug delivery includes implantable pumps.

BASIC COMPONENT OF OSMOTICALLY CONTROLLED DRUG DELIVERY SYSTEM (OSMOTIC PUMPS)

- Drug
- Osmotic agent
- Semi permeable membrane
- Plasticizers

Drugs

Characteristics of drug candidate for osmotically controlled drug delivery

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

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.

Inorganic water-soluble osmogents

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

Organic polymer osmogents

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

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: The Semi Permeable Membrane must meet some performance criteria:

- The material must possess sufficient wet strength (-10^5) and wet modulus so as to retain its dimensional integrity during the operational lifetime of the device.
- 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
- 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.
- The membrane should also be biocompatible
- Rigid and non-swelling
- Should be sufficient thick to withstand the pressure within the device.

Plasticizers

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

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

ADVANTAGES AND DISADVANTAGES OF OSMOTICALLY CONTROLLED DRUG DELIVERY SYSTEMS

Advantages[10,11]

Osmotic drug delivery system for oral and parenteral use offer distinct and practical advantage over other means of delivery. The following advantages contributed to the popularity of osmotic drug delivery systems.[12]

- They typically give a zero order release profile after an initial lag.
- Deliveries may be delayed or pulsed if desired.
- Drug release is independent of gastric pH and hydrodynamic condition.
- They are well characterized and understood.
- The release mechanisms are not dependent on drug.
- 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 git is relatively constant, at least in terms of the amount required for activation and controlling osmotically base technologies.
- Higher release rates are possible with osmotic systems compared with conventional diffusion-controlled drug delivery systems.
- The release from osmotic systems is minimally affected by the presence of food in gastrointestinal tract.
- The release rate of osmotic systems is highly predictable and can be programmed by modulating the release control parameters.

Disadvantages[10,11]

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

GENERAL MECHANISM FOR DRUG RELEASE FROM OSMOTIC PUMPS

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

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

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, L_p= 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

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

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

$$dV/dt = A/h\, L_p\, \sigma\pi = A/hk\, \pi$$

($k = L_p\sigma$ = 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)

CLASSIFICATION OF OSMOTIC DRUG DELIVERY SYSTEM

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

Osmotic Drug Delivery Devices[13,14] fall in two categories:

Implantable

The Rose and Nelson Pump
Higuchi Leeper Pump
Higuchi Theuwes pump
Implantable Miniosmotic pump

Oral osmotic Pump

- **Single chamber osmotic pump:** Elementary osmotic pump
- **Multi chamber osmotic pump:** Push pull osmotic pump, Osmotic pump with non expanding second chamber
- **Specific types:** Controlled porosity osmotic pump, Osmotic bursting osmotic pump, Liquid OROS, Delayed Delivery Osmotic device, Telescopic capsule, Oros ct (colon targeting), Sandwiched oral therapeutic system, Osmotic pump for insoluble drugs, Monolithic osmotic system and OSMAT.

Implantable osmotic drug delivery systems

For human use

More recently, osmotic principles have been applied to human parenteral therapy, resulting in the development of the DUROS® technology. These technologies allow drug delivery for site-specific as well as systemic use for delivery periods of days to 1 year.[15]

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.

The preferred site of implantation is subcutaneous placement in the inside of the upper arm. When implanted, a large, constant osmotic gradient is established between the tissue water and the osmotic engine. The engine is specifically formulated with an excess of NaCl, such that solid NaCl is present throughout the delivery period. This results in a constant osmotic gradient throughout the delivery period. In response to the osmotic gradient, water is drawn across the membrane into the osmotic engine.

Compounds delivered using DUROS® Technology: 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.

For animal models

ALZET osmotic pumps are miniature, implantable pumps used for research in mice, rats, and other laboratory animals. These infusion pumps continuously deliver drugs, hormones, and other test agents at controlled rates from one day to six weeks without the need for external connections or frequent handling. Their unattended operation eliminates the need for repeated nighttime or weekend dosing.[16]

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.

Oral osmotic drug delivery systems

As oral route is the most popular route of administration, most of the osmotic systems are developed as oral drug delivery. It is possible to deliver APIs at zero-order release rate, independent of gastric pH and hydrodynamic conditions with these osmotically controlled drug delivery systems.

These systems can be further classified in:

- Single chamber osmotic system: Elementary osmotic pump.
- Multi-chamber osmotic systems:
- Tablets with second expandable osmotic chamber: push-pull osmotic pump.
- Tablets with second non-expandable **osmotic** chamber: Two systems falls in this class i.e. Drug solution gets diluted in the second chamber before leaving device and Two separate EOP tablet formed in a single tablet
- Miscellaneous: Controlled porosity osmotic pumps, multiparticulate osmotic pump[17], osmotic bursting osmotic pump[18], Effervescent activity-based osmotic systems[19], Lipid osmotic pump.

Elementary Osmotic Pump[20-23]**:** The elementary osmotic pump is a new delivery system for drugs. It delivers the agent by an osmotic process at a controlled rate. Control resides in the:

- Water permeation characteristics of a semi permeable membrane surrounding the formulating agent
- Osmotic properties of the formulation

In its simplest embodiment the system is constructed by coating an osmotically active agent with the rate controlling semipermeable membrane. This membrane contains an orifice of critical size through which agent is delivered. The dosage form after coming into contact with aqueous fluids, imbibes water at a rate determined by the fluid permeability of the membrane and osmotic pressure of the core formulation. This osmotic imbibitions 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 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[24,25]**:** Push pull osmotic pump is a modified EOP. through, which it is possible to deliver both poorly water-soluble and highly water soluble drugs at a constant rate. This system resembles a standard bilayer coated tablet. 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. 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.

Osmotic Pump Wih Non Expanding Second Chamber[26]**:** The second category of multi-chamber devices comprises system containing a non-expanding second chamber. This group can be divided into two sub groups, depending on the function of second chamber. In one category of these devices, the second chamber is used to dilute the drug solution leaving the devices. This is useful because in some cases if the drug leaves the oral osmotic devices a saturated solution, irritation of GI tract is a risk. Example: - the problems that lead to withdrawal of osmosin, the

device consists of a normal drug containing porous tablet from which drug is released as a saturated solution. However before the drug can escape from the device it must pass through a second chamber. Water is also drawn osmotically into this chamber either because of osmotic pressure of drug solution or because the second chamber contain, water soluble diluents such as NaCl. This type of devices consist of two rigid chamber, the first chamber contains a biologically inert osmotic agent, such as sugar or a simple salt like sodium chloride, the second chamber contains the drug. In use water is drawn into both the chamber through the surrounding semi permeable membrane. The solution of osmotic agent formed in the first chamber then passes through the connecting hole to the drug chamber where it mixes with the drug solution before exiting through the micro porous membrane that form a part of wall surrounding the chamber. The device could be used to deliver relatively insoluble drugs.

Osmotic Brusting Osmotic Pump[27]**:** This system is similar to an EOP expect delivery orifice is absent and size may be smaller. When it is placed in an aqueous environment, water is imbibed and hydraulic pressure is built up inside until the wall rupture and the content are released to the environment. Varying the thickness as well as the area the semipermeable membrane can control release of drug. This system is useful to provide pulsated release.

Liquid Oral Osmotic System[28,29]**:** 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. 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.

Delayed Delivery Osmotic Device[30,31]**:** Because of their semi permeable walls, an osmotic device inherently show lag time before drug delivery begins. Although this characteristic is usually cited as a disadvantage, it can be used advantageously. The delayed release of certain drug (drugs for early morning asthma or arthritis) may be beneficial. The following text describe other means to further delay drug release.

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.[32]

Sandwiched Osmotic Tablets (SOTS)[33]**:** 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 and thus SOTS can be suitable for drugs prone to cause local irritation of the gastric mucosa.

Monolithic Osmotic System[34]**:** 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 the matrix in a serial fashion. However this system fails if more then 20 –30 volume per liter of the active agents is incorporated in to the device as above this level, significant contribution from the simple leaching of the substance take place.

Osmat[35]**:** It is a novel osmotically driven matrix system, which utilizes the hydrophilic polymers to swell, and gel in aqueous medium forming a semipermiable 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.

Controlled Porosity Osmotic Pump[36,37]**:** The pump can be made with single or multicompartment dosage form, in either form, the delivery system comprises a core with the drug surrounded by a membrane which has an asymmetric structure, i.e. comprises a thin dense skin layer supported by a porous substructure. The membrane is formed by phase inversion process controlled by the evaporation of a mixed solvent system. Membrane is permeable to water but impermeable to solute and insensitive pore forming additive dispersed throughout the wall. When exposed to water, low levels of water-soluble additive are leached from polymer materials that were permeable to water yet remained insoluble. Then resulting sponge like structure formed the controlled porosity walls of interest and was substantially permeable to both water and dissolved drug agents. 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 allued 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. (Table **1**, **2**)

Advantages of controlled porosity osmotic pumps:

- 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.
- 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.
- The delivery rate of drug from these systems is highly predictable and can be programmed by modulating the terms
- Better release rates than those obtain with conventional diffusion based drug delivery systems.
- Drug release from the OCODDSs exhibits significant *in vitro-in vivo* correlation [*ivivc*] within specific limits.

Disadvantages of controlled porosity osmotic pumps:

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

Table 1. Specification for controlled-porosity osmotic pump[37]

Material	Specification
Plasticizers and flux Regulating agents	0 to 50, preferably 0.001 to 50 parts per 100 parts of wall material
Surfactants	0 to 40, preferably 0.001to 40 parts per 100 parts of wall material
Wall thickness	1 to 1000, preferably 20 to 500 m
Microporous nature Pore forming additives	5 to 95% pores between 10a to 100 m diameter 0.1 to 60%, preferably 0.1 to 50%, by weight, based on the total weight of additive and polymer

Table 2. Specification for core of controlled-porosity osmotic pump[37]

Property	Specifications
Core loading (size)	0.05 mg to 5 g or more (include dosage forms for Humans and animals)
Osmotic pressure developed by a solution of core	8 to 500atm typically, with commonly encountered water soluble drugs and excipients
Core solubility	To get continuous, uniform release of 90% or greater of the initially loaded core mass solubility, S, to the core mass density, that is S/, must be 0.1 or lower. Typically it occurs when 10% of the initially loaded core mass saturates a volume of external fluid equal to the total volume of the initial core mass.

FACTORS AFFECTING DRUG RELEASE RATE

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[38]: 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 mixtures[39]: Mixture of citric acid and sodium bicarbonate which creates pressures in the osmotic system and ultimately controls the release rate.
- Use of cyclodextrin derivatives[40]: 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. The following table shows osmotic pressure of commonly used solutes in CR formulations[41]. (Table **3**)

Table 3. Osmotic pressures of saturated solution of commonly used osmogents

Compounds of mixture	Osmotic pressure (atm)
Lactose-Fructose	500
Dextrose-Fructose	450
Sucrose-Fructose	430
Mannitol-Fructose	415
Sodium chloride	356
Fructose	335
Lactose-Sucrose	250
Potassium chloride	245
Lactose-Dextrose	225
Mannitol-Dextrose	225
Dextrose-Sucrose	190
Mannitol-Sucrose	170
Sucrose	150
Mannitol-Lactose	130
Dextrose	82
Potassium sulphate	39
Mannitol	38
Sodium phosphate tribasic. 12H2O	36
Sodium phosphate dibasic. 7 H2O	31
Sodium phosphate dibasic. 12 H2O	31
Sodium phosphate monobasic. H2O	28
Sodium phosphate dibasic. Anhydrous	21

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

MARKETED PRODUCTS

Acutrim
- ActivePharmaceutical Ingredient: Phenylpropanolamine
- Design : Elementary osmotic pump
- Dose : 75 mg

Alpress LP
- Active Pharmaceutical Ingredient : Prazosin
- Design : Push-Pull osmotic pump
- Dose : 2.5-5 mg

Cardura XL
- Active Pharmaceutical Ingredient : Doxazosin
- Design : Push-Pull osmotic pump
- Dose : 4-8 mg

Covera HS
- Active Pharmaceutical Ingredient : Verapamil
- Design : Push -Pull osmotic pump with time delay
- Dose : 180, 240 mg

Ditropan XL
- Active Pharmaceutical Ingredient : Oxybutinin chloride
- Design : Push–Pull osmotic pump
- Dose : 5, 10 mg

Dynacirc CR
- Active Pharmaceutical Ingredient : Isradipine
- Design : Push–Pull osmotic pump
- Dose : 5, 10 mg

Efidac 24
- Active Pharmaceutical Ingredient : Pseudoephiderine
- Design : Elementary Pump
- Dose : 60 mg IR, 180 mg CR

Efidac 24
- Active Pharmaceutical Ingredient : Chlorpheniramine meleate
- Design : Elementary Pump
- Dose : 4 mg IR, 12 mg CR

Glucotrol XL
- Active Pharmaceutical Ingredient : Glipizide
- Design : Push-Pull osmotic pump
- Dose : 5, 10 mg

Sudafed 24®
- Active Pharmaceutical Ingredient : Pseudoephedrine
- Design : Elementary osmotic pump

Volmex®
- Active Pharmaceutical Ingredient : Albuterol
- Design : Elementary osmotic pump

Minipress XL®
- Active Pharmaceutical Ingredient : Prazocine
- Design : Elementary osmotic pump

Procadia XL®
- Active Pharmaceutical Ingredient : Nifedipine
- Design : Push-Pull osmotic pump

Invega®
- Active Pharmaceutical Ingredient : Paliperidone
- Design : Push-Pull osmotic pump

Viadur®
- Active Pharmaceutical Ingredient : Leuprolide acetate
- Design **:** Implantable osmotic system

Chronogesic™
- Active Pharmaceutical Ingredient : Sufentanil
- Design : Implantable osmotic system

CONCLUSION

In recent years, novel drug delivery system (NDDS) 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.

Drug delivery from these systems, to a large extent, is independent tract. 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.

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