INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACY AND CHEMISTRY

Available online at www.ijrpc.com

Review Article

OSMOTIC PUMP DRUG DELIVERY- A NOVEL APPROACH

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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. The major problem associated with conventional drug delivery system is unpredictable plasma concentrations. 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. semi permeable 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: Osmotic pump, controlled-porosity osmotic pump tablet.

Introduction Osmotically Controlled Drug Delivery System (Ocdds)

For many decades treatment of an acute disease or a chronic illness has been mostly accomplished by delivery of drugs to patients using various pharmaceutical dosage forms. Traditionally, the oral drug delivery has been popular as the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drugs. Conventional oral drug delivery systems are known to provide an immediate release of drug, in which one cannot control the release of the drug and effective concentration at the target site. The bioavailability of drug from these formulations may vary significantly, depending on factors such as physico-chemical properties of the drug, presence of excipient, various physiological factors such as the presence or absence of food, pH of the GI tract, GI motility, etc[1]. 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[2].

- Sustained and consistent blood levels within the therapeutic window
- Enhanced bioavailability
- Reduced interpatient variability
- Customized delivery profiles
- Decreased dosing frequency
- Improved patient compliance

- Reduced side effects

The drug release can be modulated by different ways but the most of novel drug delivery systems are prepared using matrix, reservoir or **osmotic** principle. In matrix systems, the drug is embedded in a polymer matrix and the release takes place by partitioning of drug into the polymer matrix and the surrounding medium. In contrast, reservoir systems have a drug core surrounded by a rate controlling membrane. The osmotic systems utilize the principles of osmotic pressure for the delivery of drugs in both the routes oral as well as parenteral[3].

Principle Of Osmosis

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. It is driven by a difference in solute concentrations across the membrane that allows passage of water, but rejects most solute molecules or ions. **Osmotic pressure** is the pressure which, if applied to the more concentrated solution, would prevent transport of water across the semi permeable membrane.

The first osmotic effect was reported by Abbe Nollet in 1748. Later in 1877, Pfeffer performed an experiment using semi-permeable membrane to separate sugar solution from pure water. He showed that the osmotic pressure of the sugar solution is directly proportional to the solution concentration and the absolute temperature. In 1886, Vant Hoff identified an underlying proportionality between osmotic pressure, concentration and temperature. He revealed that osmotic pressure is proportional to concentration and temperature and the relationship can be described by following equation.

$$\Pi = \O\, c\, RT$$

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[4].

Osmotically Controlled Drug Delivery Systems

Osmotic pressure is used as driving force for these systems to release 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.

Historical Aspects Of Osmotic Pumps

Controlled drug delivery has taken an important place in pharmaceutical development, improving the tolerability and patient compliance with prescribed dosing regimens[5-7]. Despite the predominant use of polymer-based systems, alternatives have been developed to decrease the influence of the various physiological factors that occur following food intake or that are dependent on patient age[8-10]. One of the most promising technologies is the oral osmotically driven system (OODS)[10-12]. Nevertheless, over the past 30 years, the development of OODS technologies has been accompanied by controversies around product safety and concerns regarding the benefit/cost-of-good ratio. It is, therefore, interesting to begin this paper by reviewing the key milestones in OODS development. Oral osmotically driven systems have primarily evolved from being device concepts for the delivery of veterinary medicines, namely Rose-Nelson[13], Higuchi-Leeper[14] (fig.1) and Higuchi-Theeuwes pumps[15] (fig 2). 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 'semipermeable' membrane controlling the drug delivery rate . Relatively complex and scalable with technical difficulties, a major milestone was achieved in 1974 with the description by Theeuwes and Alza's co-workers of a tablet design[16-17] composed of a compressed tablet-core surrounded by a semipermeable membrane with a single passageway (orifice), the so-called elementary osmotic pump (EOP). This design adaptation for human use was conveniently processable using standard tabletting and coating procedures and equipment[18]. The first two products indomethacin, Osmosin[19] and phenylpropanolamine, AcutrimTM[20], were launched in the 1980s. In contrast to the originally anticipated business success[21-23], Osmosin_ had to be withdrawn from the market due to severe side effects such as GI irritation and perforation of the intestinal wall[24-26]. This opened a crucial debate on (i) the safety of administering non-degradable systems such as OODS per-os, (ii) 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 (iii) 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[27-30], 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[31-33] from 1990 to 1995. 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, then 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. 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. Such a strategy should address the three fundamental questions, which are as follows:

– Is the OODS technology safe for administering a specific drug?
– Does the drug release profile over time match the target?
(Desired) pharmacokinetics in the patient?
– To what extent is it beneficial in terms of the patient's compliance?

HIGUCHI-LEEPER PUMP

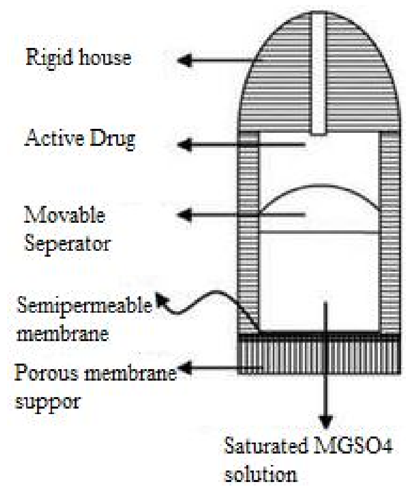

Fig. 1: Higuchi-Leeper pump

The 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. The pump is activated when it is swallowed or implanted in the body. This pump consists of a rigid housing, and the semipermeable membrane is supported on a perforated frame. It has a salt chamber containing a fluid solution with excess solid salt. Recent modification in Higuchi-Leeper pump accommodated pulsatile drug delivery. The pulsatile release was achieved by the production of a critical pressure at which the delivery orifice opens and releases the drug.

HIGUCHI-THEEUWES PUMP

Further simplified variant of Rose-Nelson pump was developed by Higuchi and Theeuwes. This pump comprises a rigid, rate controlling outer semipermeable membrane surrounding a solid layer of salt coated on the inside by an elastic diaphragm and on the outside by the membrane. In use, water is osmotically drawn by the salt chamber, forcing drug from the drug chamber.

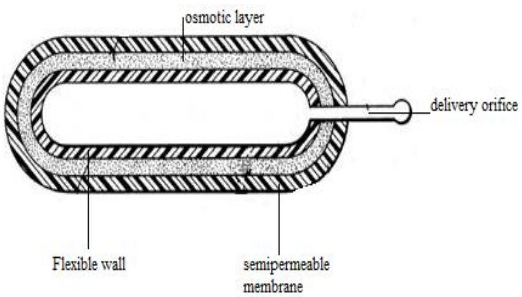

Fig. 2: Higuchi-Theeuwes pump

In 1975, the major leap in **osmotic** delivery occurred as the elementary **osmotic** pump for oral delivery of drugs was introduced. The pump consists of an **osmotic** core containing the drug, surrounded by a semipermeable membrane with a delivery orifice. When this pump is exposed to water, the core imbibes water osmotically at a controlled rate, determined by the membrane permeability to water and by the osmotic pressure of the core formulation. As the membrane is non-expandable, the increase in volume caused by the imbibitions of water leads to the development of hydrostatic pressure inside the tablet. This pressure is relieved by the flow of saturated solution out of the device through the delivery orifice. This process continues at a constant rate until the entire solid agent inside the tablet has been dissolved and only a solution filled coating membrane is left. This residual dissolved agent continues to be delivered at a declining rate until the osmotic pressure inside and outside the tablet is equal. Normally, the EOP delivers 60-80% of its contents at a constant rate, and there is a short lag time of 30-60 min as the system hydrates before zero order delivery from the EOP is obtained.

Apart from oral **osmotic** pumps, the development of miniature **implantable osmotic pumps** in the mid-1970s was a major breakthrough to deliver wide range of drugs and hormones, including peptides at constant and programmed rate in mice, rat and larger animals. These implants provide a convective stream of drug solution that can be directed through suitable catheter connections to sites in the animal remote from itself. Most recently the implantable pumps for human use are developed to deliver the drug for targeting or systemic application.

Classification Of Osmotic Drug Delivery Systems

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

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. 1) Drug solution gets diluted in the second chamber before leaving device and 2) Two separate EOP tablet formed in a single tablet
- Miscellaneous: Controlled porosity osmotic pumps, multiparticulate osmotic pump[34], osmotic bursting osmotic pump[35], Effervescent activity-based osmotic systems[36], Lipid osmotic pump[37].

Implantable Osmotic Drug Delivery System

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[38].

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.
Applications, the preferred site of implantation are 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.

Mechanism For Drug Release From Osmotic Pumps

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

$dM / dt = dV / dt \times c$

Where,
dM / dt= mass release
dV / dt= volumetric pumping rate
c = concentration of drug
But,
$dV / dt = (A/ h)L_p (\sigma \Delta\Pi - \Delta p)$
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).

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[39]: 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[40]: Mixture of citric acid and sodium bicarbonate which creates pressures in the **osmotic** system and ultimately controls the release rate.
- Use of cyclodextrin derivatives[41]: 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[42]: Solubility modifier excipient used in form of mini-tablet coated with rate controlling membrane.
- Resin Modulation approach[43]: 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[44].
- Co-compression of drug with excipients [45-46]: 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[47].

Compound or mixture	Osmotic pressure
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-sulfate	39
Mannitol	38
Sodium Phosphate tribasic.12H_2O	36
Sodium-Phosphate dibasic.7H_2O	31
Sodium-phosphate dibasic.12H_2O	31
Sodium-phoasphate dibasic anhydrous	29
Sodium-phosphate monobasic.H_2O	28

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[48,49].
- Indentation that is not covered during the coating process[50]: 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 membrane.

Basic components of osmotic systems

Drug

which have short biological half-life and which is used for prolonged treatment are ideal candidate for **osmotic** systems. Various drug candidates such as Diltiazem HCl[51], Carbamazepine, Metoprolol[52], Oxprenolol, Nifedipine[53], Glipizide[54], etc are formulated as osmotic delivery.

Osmotic Agent

Osmotic components usually are ionic compounds consisting of either inorganic salts or hydrophilic polymers. Some of the **osmotic** agents that can be used for such systems are classified below. Different type of osmogents can be used for such systems are categorized as water-soluble salts of inorganic acids like magnesium chloride or sulfate; lithium, sodium, or potassium chloride; sodium or potassium hydrogen phosphate; water-soluble salts of organic acids like sodium and potassium acetate, magnesium succinate, sodium benzoate, sodium citrate, sodium ascorbate; Carbohydrates like mannose, sucrose, maltose lactose; water-soluble amino acids and organic polymeric osmogents, etc.

Semipermeable Membrane
An important part of the **osmotic** drug delivery system is the SPM housing. Therefore, the polymeric membrane selection is key to **osmotic** delivery formulation. The membrane must possess certain performance criteria such as:

- Sufficient wet strength and water permeability
- Should be biocompatible
- Rigid and non-swelling
- Should be sufficient thick to withstand the pressure within the device.

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[55].

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 Of Osmotic Drug Delivery Systems
Osmotic drug delivery systems for oral and parenterals use offer distinct and practical advantages over other means of delivery. The following advantages have contributed to the popularity of **osmotic** drug delivery systems[55].

- The delivery rate of zero-order is achievable with **osmotic** systems.
- Delivery may be delayed or pulsed, if desired.
- 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.
- For oral **osmotic** systems, drug release is independent of gastric pH and hydrodynamic conditions.
- The release from **osmotic** systems is minimally affected by the presence of food in gastrointestinal tract.
- A high degree of in vivo- in vitro correlation (IVIVC) is obtained in **osmotic** system.

MARKETED PRODUCT
Elementary Osmotic Pump

Brand Name	API
Efidac 24®	Chlorpheniramine
Acutrim ®	Phenylpropanolamine
Sudafed 24®	Pseudoephedrine
Volmax ®	Albuterol
Minipress XL®	Prazocine

Push-Pull Osmotic Systems

Ditropan XL ®	Oxybutynin chloride
Procardia XL®	Nifedipine
Glucotrol ®	Glipizide
Covera HS ®	Verapamil HCl
DynaCirc CR®	Isradipine[56]
Invega®	Paliperidone[57]

Implantable Osmotic Systems

Viadur®	Leuprolide acetate
Chronogesic™	Sufentanil

CONCLUSIONS

It can be concluded that the oral controlled-porosity osmotic pump system comprising a compressed tablet coated with a semi permeable membrane is simple to prepare with no drilling required and can be used in the field of controlled delivery of drugs. Development efforts of oral osmotically driven systems (OODSs) during recent years have been very dynamic with the emergence of new technologies and products. With the expiration of the OODS primary patents and the increasing demand of health authorities for improved patient treatment compliance and tolerability, the OODS is primed to increase their market with in oral modified-release dosage forms. 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.

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