ISSN: 2277- 7695
CODEN Code: PIHNBQ
ZDB-Number: 2663038-2
IC Journal No: 7725

ISSN 2277-7695

Vol. 1 No. 7 2012
Online Available at www.thepharmajournal.com

THE PHARMA INNOVATION

Osmotic-Controlled Release Oral Delivery System: An Advanced Oral Delivery Form

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The osmotic-controlled release oral delivery system, OROS, is an advanced drug delivery technology that uses osmotic pressure as the driving force to deliver pharmacotherapy, usually once-daily, in several therapeutic areas. Oral route is one of the most extensively used routes of drug administration because of its obvious advantages of ease of administration, improved patient compliance and convenience. The main clinical benefits of OROS are their ability to improve treatment tolerability and patient compliance. These advantages are mainly driven by the capacity to deliver drugs in a sustained manner, independent of the drug chemical properties, of the patient's physiological factors or concomitant food intake. However, access to these technologies has been restricted by the crowded patent landscape and manufacturing challenges. In this review, we intend to give an overview of the OROS development in the last 30 years, detailing the technologies, specific products and their clinical use. General guidance on technology selection is described in light of the recent advances in the field. The clinical performance of these technologies is also discussed, with a focus on food effects and the in vivo–in vitro correlation. Special attention is paid to safety given the controversial case study of Osmosin. Overall, oral osmotically driven systems appear to be a promising technology for product life-cycle strategies.

Keyword: Osmotic-Controlled Release, Oral Delivery System, Technology

INTRODUCTION: Osmotic systems for controlled drug-delivery applications are well established, both in human pharmaceuticals and in veterinary medicine. Several one compartment and two-compartment osmotic systems have been reviewed previously [1–4]. In addition, a large body of patent literature exists that describes new and novel osmotic systems [5]. The historical development of osmotic systems includes seminal contributions such as the Rose–Nelson pump [6], the Higuchi–Leeper pumps [7–10], the AlzetR and OsmetR systems [11], the elementary osmotic pump [12], and the push-pull or GITSR system [13–15]. Recent advances include the development of the controlled porosity osmotic pump [16–18] systems based on asymmetric

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membranes [19–23], and other approaches [24–28]. Osmotic drug-delivery systems suitable for oral administration typically consist of a compressed tablet core that is coated with a semipermeable membrane coating. This coating has one or more delivery ports through which a solution or suspension of the drug is released over time. The core consists of a drug formulation that contains an osmotic agent and a water swellable polymer. The rate at which the core absorbs water depends on the osmotic pressure generated by the core components and the permeability of the membrane coating. As the core absorbs water, it expands in volume, which pushes the drug solution or suspension out of the tablet through one or more delivery ports. The key distinguishing feature of osmotic drug delivery systems (compared with other technologies used in controlled-release formulations) is that they release drug at a rate that is independent of the pH and hydrodynamics of the external dissolution medium. The result is a robust dosage form for which the in vivo rate of drug release is comparable to the in vitro rate, producing an excellent in vitro/in vivo correlation. Another key advantage of the present osmotic systems is that they are applicable to drugs with a broad range of aqueous solubilities. Depending on aqueous solubility, the drug is released either as a solution or as a suspension. Of course, any drug released as a suspension must dissolve in the in vivo environment and overcome biological barriers before it becomes systemically available [12,16,22,28].

Table 1: Historical aspects of osmotic pumps [29-32]

YEAR	COMMENTS	REFERENCE
1748	First report of osmosis	(Banker, 1987)
1877	Quantitative measurement of osmotic pressure	(AMartin, 1993)
1955	First osmotic pump by Rose and Nelson	(Rose etal, 1995)
1973	Higuchi-leeper introduced a new version of Rose and Nelson pump with certain modifications	(Santus etal, 1995)
1973	Osmotically powdered agent dispense device with filling means	(Theeuwes, 1984)
1975	Major milestone in the field of osmotic drug delivery-introduced the first oral osmotic pump i.e. E.O.P	(Cortese etal, 1982)
1976	Patent granted on the design of oral osmotic pump	(Theeuwes etal, 1984)
1982	Patent issue for an osmotic system which consist of a layer of a fluid swell able hydrogel	(Cortese etal,1984)
1984	First report of combination therapy by use of push-pull osmotic pump	(Theeuwes etal, 1984)
1985	Controlled porous osmotic pump was developed	(Zentner etal, 1991)
1986	Patent issue claiming a delivery for controlled administration of drug to ruminants	(Mishra etal, 2006)
1989	Developed push-pull osmotic pump for Nifedipine by Pfizer	(Mishra etal, 2006) (Wilson etal, 2000)
1995	Patent to an osmotic dosage form for liquid drug delivery	(Mishra etal, 2006)
1999	Asymmetric membrane capsule was introduced	(Mishra etal, 2006)
2000	DUROS Leurpolid implants i.e. Viadur approved as first implantable osmotic pump for humans by US FDA	(Mishra etal, 2006)
2001	Patent granted for dosage form comprising liquid drug formulation that can self emulsify to enhance the solubility, dissolution and bioavailability of drug	(Mishra etal, 2006)
2003	First report osmotic floating system	(Mishra etal, 2006)

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 [14,15].

1. The delivery rate of zero-order is achievable with osmotic systems.
2. Delivery may be delayed or pulsed, if desired.
3. Higher release rates are possible with osmotic systems compared with conventional diffusion-controlled drug delivery systems.
4. The release rate of osmotic systems is highly predictable and can be programmed by modulating the release control parameters.
5. For oral osmotic systems, drug release is independent of gastric pH and hydrodynamic conditions.
6. The release from osmotic systems is minimally affected by the presence of food in gastrointestinal tract.
7. A high degree of in vivo- in vitro correlation (IVIVC) is obtained in osmotic systems.

LIMITATIONS OF OSMOTIC DRUG DELIVERY SYSTEMS [16,17]

1. Special equipment is required for making an orifice in the system.
2. Residence time of the system in the body varies with the gastric motility and food intake.
3. It may cause irritation or ulcer due to release of saturated solution of drug.

KEY PARAMETERS THAT INFLUENCE THE DESIGN OF OSMOTIC CONTROLLED DRUG DELIVERY SYSTEMS

➢ Orifice size

To achieve an optimal zero-order delivery profile, the cross-sectional area of the orifice must be smaller than a maximum size to minimize drug delivery by diffusion through the orifice. Furthermore, the area must be sufficiently large, above a minimum size to minimize hydrostatic pressure buildup in the system. Otherwise, the hydrostatic pressure can deform the membrane and affect the zero-order delivery rate. Therefore, the cross-sectional area of the orifice should be maintained between the minimum and maximum values [18,19].

Methods to create a delivery orifice in the osmotic tablet coating are:

1. Mechanical drill
2. Laser drill- This technology is well established for producing sub-millimeter size hole in tablets. Normally, CO2 laser beam (with output wavelength of 10.6μ) is used for drilling purpose, which offers excellent reliability characteristics at low costs [20,21].
3. Indentation that is not covered during the coating process [22]: 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.
4. Use of leachable substances in the semipermeable coating : e.g. controlled porosity osmotic pump

➢ Solubility

The release rate depends on the solubility of the solute inside the drug delivery system. Therefore, drugs should have sufficient solubility to be delivered by osmotic delivery. In the case of low solubility compounds, several alternate strategies may be employed. Broadly, the approaches can be divided into two categories. First, swellable polymers can be added that result in the delivery of poorly soluble drugs in the form of a suspension [23]. Second, the drug solubility can be modified employing different methods such as compression of the drug with other excipients, which improve the solubility [24]. For example, cyclodextrin can be included in the formulation to

enhance drug solubility [25]. Additionally, alternative salt forms of the drug can be employed to modulate solubility to a reasonable level. In one case, the solubility of oxprenolol is decreased by preparing its succinate salt so that a reduced saturation concentration is maintained [26].

Table 2: Osmotic pressure of common mixtures

Compounds of mixture	Osmotic Pressure
Lactose-Fructose 500	500
Dextrose-Fructose 450	450
Sucrose-Fructose 430	430
Mannitol-Fructose 415	415
Sodium chloride 356	356
Fructose 335	335
Lactose-Sucrose 250	250
Potassium chloride 245	245
Lactose-Dextrose 225	225
Mannitol-Dextrose 225	225
Dextrose-Sucrose 190	190
Mannitol-Sucrose 170	170
Sucrose 150	150
Mannitol-Lactose 130	130
Dextrose 82	82
Potassium sulphate 39	39
Mannitol 38	38

➢ Osmotic pressure

The osmotic pressure (π) directly affects the release rate. To achieve a zero-order release rate, it is essential to keep (π) constant by maintaining a saturated solute solution. Many times, the osmotic pressure generated by the saturated drug solution may not be sufficient to achieve the required driving force. In this case, other osmotic agents are added that enhance osmotic pressure. For example, addition of bicarbonate salt not only provides the necessary osmotic gradient but also prevents clogging of the orifice by precipitated drug by producing an effervescent action in acidic media [27,30].

➢ Semipermeable membrane

Since the semipermeable membrane is permeable to water and not to ions, the release rate is essentially independent of the pH of the environment. Additionally, the drug dissolution process takes place inside the delivery system, completely separated from the environment [26].

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, Carbamazepine, Metoprolol, Oxprenolol, Nifedipine, Glipizide etc are formulated as osmotic delivery.

Semipermeable membrane

An important part of the osmotic drug delivery system is the semipermeable membrane housing. Therefore, the polymeric membrane selection is key to the osmotic delivery formulation. The membrane should possess certain characteristics, such as impermeability to the passage of drug and other ingredients present in the compartments. The membrane should be inert and maintain its dimensional integrity to provide a constant osmotic driving force during drug delivery [28]. 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 [29].

Osmotic agent

Osmotic agents maintain a concentration gradient across the membrane. They also generate a driving force for the uptake of water and assist in maintaining drug uniformity in the hydrated formulation. Osmotic components usually are ionic compounds consisting of either inorganic salts or hydrophilic polymers. Osmotic agents can be any salt such as sodium chloride, potassium chloride, or sulfates of sodium or potassium and lithium. Additionally, sugars such as glucose, sorbitol, or sucrose or inorganic salts of carbohydrates can act as osmotic agents. The polymers may be formulated along with poly(cellulose), osmotic solutes, or colorants such as ferric oxide. Swellable polymers such as poly(alkylene oxide), poly(ethylene oxide), and poly (alkalicarboxymethylcellulose) are also included in the push layer of certain osmotic systems. Further, hydrogels such as Carbopol (acidic carboxypolymer),Cyanamer (polyacrylamides), and Aqua-Keeps (acrylate polymer polysaccharides composed of condensed glucose units such as diester cross-linked polygluran) may be used.

Flux regulators

Delivery systems can be designed to regulate the permeability of the fluid by incorporating fluxregulating agents in the layer. Hydrophilic substances such as polyethethylene glycols (300 to 6000 Da), polyhydric alcohols, polyalkylene glycols, and the like improve the flux, whereas hydrophobic materials such as phthalates substituted with an alkyl or alkoxy (e.g., diethyl phthalate or dimethoxy ethylphthalate) tend to decrease the flux. Insoluble salts or insoluble oxides, which are substantially water-impermeable materials, also can be used for this purpose [8].

Wicking agent

A wicking agent is defined as a material with the ability to draw water into the porous network of a delivery device. A wicking agent is of either swellable or non-swellable nature. They are characterized by having the ability to undergo physisorption with water. Physisorption is a form of absorption in which the solvent molecules can loosely adhere to surfaces of the wicking agent via Vander Waals interactions between the surface of the wicking agent and the adsorbed molecule. The function of the wicking agent is to carry water to surfaces inside the core of the tablet, thereby creating channels or a network of increased surface area. Materials, which suitably for act as wicking agents include colloidal silicon dioxide, kaolin, titanium dioxide, alumina, niacinamide, sodium lauryl sulphate (SLS), low molecular weight poly vinyl pyrrolidone (PVP), m-pyrol, bentonite, magnesium aluminium silicate, polyester and polyethylene.

Pore forming agent

These agents are particularly used in the pumps developed for poorly water soluble drug and in the development of controlled porosity or multiparticulate osmotic pumps. These poreforming agents cause the formation of microporous membrane. The microporous wall may be formed in situ by a pore-former by its leaching during the operation of the system. The pore formers can be inorganic or organic and solid or liquid in nature.

For example, alkaline metal salts such as sodium chloride, sodium bromide, potassium chloride, potassium sulphate, potassium phosphate etc., alkaline earth metals such as calcium chloride and calcium nitrate, carbohydrates such as sucrose, glucose, fructose, mannose, lactose, sorbitol, mannitol and, diols and polyols such as poly hyric alcohols and polyvinyl pyrrolidone can be used as pore forming agents.

Coating solvent

Solvents suitable for making polymeric solution that is used for manufacturing the wall of the osmotic device include inert inorganic and organic solvents that do not adversely harm the core, wall and other materials. The typical solvents include methylene chloride, acetone, methanol, ethanol, isopropyl alcohol, butyl alcohol, ethyl acetate, cyclohexane, carbon tetrachloride, water etc. The mixtures of solvents such as acetone-methanol (80:20), acetone-ethanol (80:20), acetone-water (90:10),

methylene chloride-methanol (79:21), methylene chloride-methanol-water (75:22:3) etc. can be used [30].

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 [8]. Some of the plasticizers used are as below:

1. Polyethylene glycols
2. Ethylene glycol monoacetate; and
3. diacetate- for low permeability
4. Tri ethyl citrate
5. Diethyl tartarate or Diacetin- for more permeable films

TYPES OF OSMOTIC PUMPS

Based on their design and the state of active ingredient, osmotic delivery systems can be classified as follows:

1. Osmotic delivery systems for solids

a. Type I: Single compartment. In this design, the drug and the osmotic agent are located in the same compartment and are surrounded by the semipermeable membrane (SPM). Both the core components are dissolved by water, which enters the core via osmosis. A limitation is the dilution of drug solution with the osmotic solution, which affects the release rate of the drug from the system. Additionally, water-incompatible or water-insoluble drugs cannot be delivered effectively from a singlecompartment configuration.

b. Type II: Multiple compartments. In this design, drug is separated from the osmotic compartment by an optional flexible film, which is displaced by the increased pressure in the surrounding osmotic compartment, which, in turn, displaces the drug solution or suspension. The type II system inherently has greater utility than type I systems and can deliver drugs at a desired rate independent of their solubilities in water. One main advantage of these systems is their ability to deliver drugs that are incompatible with commonly used electrolytes or osmotic agents.

2. Osmotic delivery systems for liquids.

Active ingredients in liquid form are difficult to deliver from controlled release platforms because they tend to leak in their native form. Therefore, liquid active agents typically are enclosed in a soft gelatin capsule, which is surrounded by an osmotic layer that, in turn, is coated with a semipermeable membrane. When the system takes up water from its surroundings, the osmotic layer squeezes the innermost drug reservoir. The increasing internal pressure displaces the liquid from the system via a rupturing soft gelatin capsule [8].

Principal Oral Osmotically Driven technologies and designs [33-43]

A. Unitary Core Osmotic Pumps

a) Elementary Osmotic Pump

- **i. Self emulsified elementary osmotic pump**
- **ii. Over coated elementary osmotic pump**
- **iii. Effervescent elementary osmotic pump**

b) Controlled porosity osmotic pump

B. Multilayer Osmotic Pumps

- **i. Push pull osmotic pump**
- **ii. Push stick osmotic pump**
- **iii. Muco-adhesive osmotic pump**

C. Capsule based osmotic pumps

- **i. Chronset**
- **ii. Osmet**
- **iii. Assymetric membrane osmotic pump**
- **iv. Liquid osmotic system (L-OROS)**

CONCLUSION

In osmotic delivery systems, osmotic pressure provides the driving force for drug release. Increasing pressure inside the dosage form from water incursion causes the drug to release from the system. The major advantages include precise control of zero-order or other patterned release over an extended time period—consistent release rates can be achieved irrespective of the environmental factors at the delivery site. Controlled delivery via osmotic systems also may reduce the side-effect profile by moderating the blood plasma peaks typical of conventional (e.g., instant release) dosage forms. Moreover, since efficacious plasma levels are maintained longer in osmotic systems, avoidance of trough plasma levels over the dosing interval is possible. However, a complex manufacturing process and higher cost compared with conventional dosage forms limit their use. Although not all drugs available for treating different diseases require such precise release rates, once-daily formulations based on osmotic principles are playing an increasingly important role in improving patient compliance. Therefore, most of the currently marketed products are based on drugs used in long-term therapies for diabetes, hypertension, attention-deficit disorder, and other chronic disease states. Besides oral osmotic delivery systems, implants that work on osmotic principles are promising for delivery of a wide variety of molecules with a precise rate over a long period of time. Further, with the discovery of newer and potent drugs by the biotechnology industry, the need to deliver such compounds at a precise rate certainly will pave the way for osmotic delivery systems to play an increasingly important role in drug delivery.

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