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REVIEW ARTICLE

An Overview on Osmotic Controlled Drug Delivery System

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ABSTRACT

This paper reviews constructed drug delivery systems applying osmotic principles for controlled drug release from the formulation. Osmotic devices which are tablets coated with walls of controlled porosity are the most promising strategy based systems for controlled drug delivery. In contrast to common tablets, these pumps provide constant (zero order) drug release rate. 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. The main clinical benefits of oral osmotic drug delivery system 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 following food intake. This review brings out the theoretical concept of drug delivery, history, advantages and disadvantages of the delivery systems, types of oral osmotic drug delivery systems, factors affecting the drug delivery system and marketed products.

KEYWORDS

Osmosis, osmotic pressure, Osmotic pump, Zero-order release, Oral osmotic systems.

INTRODUCTION

Conventional drug delivery systems have slight 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 controlled or modified release drug delivery systems. They include dosage forms for oral and transdermal administration as well as injectable and implantable systems. For most of drugs, oral route remains as the most acceptable route of administration. Certain molecules may have low oral bioavailability because of solubility or permeability limitations. Development of an extended release dosage form also requires reasonable absorption throughout the gastro-intestinal tract (GIT). Among the available techniques to improve the bioavailability of these drugs fabrication of osmotic drug delivery system is the most appropriate one. Osmotic drug delivery systems release the drug with the zero order kinetics which does not depend on the initial concentration and the physiological factors of GIT[1].

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Osmosis

Osmosis refers to the process of movement of solvent molecules from lower concentration to higher concentration across a semi permeable membrane[2].

Osmotic pressure

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. 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[2].

Principles of Osmosis[3,4,5]

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 cm2, 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.

Historical Background

About 75 years after discovery of the osmosis principle, it was first used in the design of drug delivery systems[6]. Rose and Nelson, the Australian scientists, were initiators of osmotic drug delivery. In 1955, they developed an implantable pump, which consisted of three chambers: a drug chamber, a salt chamber contains excess solid salt, and a water chamber. The drug and water chambers are separated by rigid semipermeable membrane. The difference in osmotic pressure across the membrane moves water from the water chamber into the salt chamber. The volume of the salt chamber increases because of this water flow, which distends the latex diaphragm separating the salt and drug chambers, thereby pumping drug out of the device. The design and mechanism of this pump is comparable to modern push-pull osmotic pump. The major disadvantage of this pump was the water chamber, which must be charged before use of the pump. The pumping rate of this push-pull pump is given by the equation.

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

In general, this equation, with or without some modifications, applies to all other type of osmotic systems. Several simplifications in Rose-Nelson pump were made by Alza Corporation in early 1970s. 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[7].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[8].

Advantages & Disadvantages of Osmotic Controlled Drug Delivery Systems

Advantages[9-13]

- ✓ 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[9,10,14,15]

- ✓ Special equipment is required for making an orifice in the system.
- ✓ It may cause irritation or ulcer due to release of saturated solution of drug
- ✓ Dose dumping
- ✓ Retrival therapy is not possible in the case of unexpected adverse events.
- ✓ 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

Basic Components of Osmotic Controlled Drug Delivery Systems

Drug [1,16]

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.

Basic Criterion for Drug Selection:

- ✓ Short biological Half-life (2- 6 hrs)
- ✓ High potency
- ✓ Required for prolonged treatment

Semipermeable Membrane

Since the membrane in osmotic systems is semipermeable in nature, any polymer that is permeable to water but impermeable to solute can be selected[17]. Cellulose acetate is a commonly employed semipermeable polymer for the preparation of osmotic pumps. It is available in different acetyl content grades.

Particularly, acetyl content of 32% and 38% is widely used. Acetyl content is described by the degree of substitution (DS), that is, the average number of hydroxyl groups on the anhydrous glucose unit of the polymer replaced by substituting group. Some of the polymers that can be used for above purpose include cellulose esters such as cellulose acetate, cellulose diacetate, cellulose triacetate, cellulose propionate, cellulose acetate butyrate, and cellulose ethers like ethyl cellulose[18]. Apart from cellulose derivatives, some other polymers such as agar acetate, amylose triacetate, betaglucan acetate, poly (vinyl methyl) ether copolymers, poly (orthoesters), poly acetals and selectively permeable poly(glycolic acid), poly(lactic acid) derivatives, and Eudragits can be used as semipermeable film-forming materials[19]. The permeability is the important criteria for the selection of semipermeable polymers[20].

Hydrophilic and Hydrophobic Polymers

These polymers are used in the formulation development of osmotic systems for making drug containing matrix core. The highly water soluble compounds can be co entrapped in hydrophobic matrices and moderately water soluble compounds can be co-entrapped in hydrophilic matrices to obtain more controlled release. Generally, mixtures of both hydrophilic and hydrophobic polymers have been used in the development of osmotic pumps of water-soluble drugs[21]. The selection is based on the solubility of the drug as well as the amount and rate of drug to be released from the pump. The polymers are of either swellable or non swellable nature. Mostly, swellable polymers are used for the pumps containing moderately water-soluble drugs. Since they increase the hydrostatic pressure inside the pump due to their swelling nature, the non swellable polymers are used in case of highly water-soluble drugs[2]. Ionic hydrogels such as sodium carboxy methyl cellulose are preferably used because of their osmogenic nature. More precise controlled release of drug scan be achieved by incorporating these polymers into the formulations. Hydrophilic polymers such as hydroxy ethylcellulose, carboxy methylcellulose, hydroxy propyl methyl cellulose, high-molecular-weight poly(vinyl pyrrolidone), and hydrophobic polymers such as ethyl cellulose and wax materials can be used for this purpose[14].

Wicking Agents

A wicking agent is defined as a material with the ability to draw water into the porous network of a delivery device. The wicking agents are those agents which help to increase the contact surface area of the drug with the incoming aqueous fluid. The use of the wicking agent helps to enhance the rate of drug released from the orifice of the drug. A wicking agent is of either swellable or non swellable nature[22]. 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 Van der 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 [23].The examples are colloidal silicon dioxide, PVP and Sodium lauryl sulfate.

Solubilizing Agent

For osmotic drug delivery system, highly water-soluble drugs would demonstrate a high release rate that would be of zero order. Thus, many drugs with low intrinsic water solubility are poor candidates for osmotic delivery. However, it is possible to modulate the solubility of drugs within the core. Addition of solubilizing agents into the core tablet dramatically increases the drug solubility[24]. Non swellable solubilizing agents are classified into three groups,

(i) Agents that inhibit crystal formation of the drugs or otherwise act by complexation with the drugs (e.g., PVP, poly (ethylene glycol) (PEG 8000) and β-cyclodextrin),

(ii) a micelle-forming surfactant with high HLB value, particularly nonionic surfactants (e.g., Tween 20, 60,and 80, polyoxy ethylene or poly

ethylene containing surfactants and other long-chain anionic surfactants such as SLS),

(iii) Citrate esters (e.g., alkyl esters particularly triethylcitrate) and their combinations with anionic surfactants. The combinations of complexing agents such as polyvinyl pyrrolidone (PVP) and poly (ethylene glycol) with anionic surfactants such as SLS are mostly preferred.

Osmogens

Osmogens are essential ingredient of the osmotic formulations. Upon penetration of biological fluid into the osmotic pump through semipermeable membrane, osmogens are dissolved in the biological fluid, which creates osmotic pressure buildup inside the pump and pushes medicament outside the pump through delivery orifice. They include inorganic salts and carbohydrates. Mostly, potassium chloride, sodium chloride, and mannitol used as osmogens. Generally combinations of osmogens are used to achieve optimum osmotic pressure inside the system (Table 1)[25].

Surfactants

Surfactants are particularly useful when added to wall-forming material. They produce an integral composite that is useful for making the wall of the device operative.

The surfactants act by regulating the surface energy of materials to improve their blending into the composite and maintain their integrity in the environment of use during the drug release period. Typical surfactants such as poly oxy ethylenated glycerylrecinoleate, polyoxy ethylenated cast or oil having ethylene oxide, glyceryllaurates, and glycerol (sorbitonoleate, stearate, or laurate) are in corporate into the formulation.

Coating Solvents[1]

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 and other materials. The typical solvents include methylene chloride, acetone, methanol, ethanol, isopropyl alcohol, butyl alcohol, ethylacetate, cyclohexane, carbon tetrachloride, and water. 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) can be used.

Plasticizers

In pharmaceutical coatings, plasticizers, or low molecular weight diluents are added to modify the physical properties and improve film-forming characteristics of polymers.

Table 1: Some of the commercially used osmotic agents along with their osmotic pressure[26,27]

Compound	Osmotic pressure (atm)	Mixture	Osmotic pressure (atm)
Sodium chloride	356	Lactose – Fructose	500
Fructose	355	Lactose - sucrose	250
Potassium chloride	245	Lactose – Dextrose	225
Sucrose	150	Dextrose – Sucrose	190
Xylitol	104	Mannitol - Sucrose	170
Sorbitol	84	Sodium phosphate dibasic 12H2O	31
Dextrose	82	Sodium phosphate Monobasic .H2O	28

Plasticizers can change visco elastic behavior of polymers significantly[28]. Plasticizers can turn a hard and brittle polymer into a softer, more pliable material, and possibly make it more resistant to mechanical stress[11].Plasticizers lower the temperature of the second order-phase transition of the wall or the elastic modules of the wall and also increase the workability, flexibility, and permeability of the coating solvents. Generally from 0.001 to 50 parts of a plasticizer or a mixture of plasticizers are incorporated into100 parts of costing materials. PEG-600, PEG-200, triacetin(TA), dibutyl sebacate, ethylene glycolmono acetate, ethylene glycol diacetate, triethyl phosphate, and diethyl tartrate used as plasticizer in formulation of semipermeable membrane[29,30].

Pore-Forming Agents

These agents are particularly used in the pumps developed for poorly water-soluble drugs and in the development of controlled porosity or multi particulate osmotic pumps[31]. These pore-forming agents cause the formation of micro porous membrane. The micro porous 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, and so forth, alkaline earth metals such as calcium chloride and calcium nitrate, carbohydrates such as sucrose, glucose, fructose, mannose, lactose, sorbitol, and mannitol, and diols and polyols such as poly hydricalcohols, polyethylene glycols, and polyvinyl pyrrolidone can be used as pore-forming agents[32]. Triethyl citrate (TEC) and triacetin (TA) are also used to create pore in the membrane. Membrane permeability to the drug is further increased addition of HPMC or sucrose[33].

Flux Regulators

Flux regulating agents or flux enhancing agent or flux decreasing agent are added to the wall forming material. Delivery systems can be designed to regulate the permeability of the fluid by incorporating flux regulating agents in the layer. Hydrophilic substances such as poly ethethylene glycols (300 to 6000 Da), polyhydric alcohols, poly alkylene glycols, and the like improve the flux, whereas hydrophobic materials such as phthalates substituted with an alkyl or alkoxy (e.g., diethyl phthalate or dimethoxyethyl phthalate) tend to decrease the flux. Insoluble salts or insoluble oxides, which are substantially water-impermeable materials, also can be used for this purpose[1,16].

Factors Affecting the Performance of Osmotic Drug Delivery System

There are following factors which should be considered while designing an EOP. These factors are also applicable to other osmotic drug delivery systems:

Membrane Thickness

A principle factor controlling the rate of penetration of water into the dispenser is the thickness of the membrane. The permeability of water into the membrane can be enhanced by the choice of a suitable type of the membrane material. The time of release of the active constituent can be easily varied by as much as 1000 fold based upon the thickness of the membrane. In general the rate of drug release can be achieved by varying the membrane material, while small change up to a five percent can be best achieve by varying the thickness of the membrane[22].

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[33].

Type of Membrane and Characteristics

Drug release from an osmotic system is largely independent of the pH and agitation intensity of GIT tract[34]. This is because of its selective water permeable membrane and effective isolation of dissolution process of drug core from the gut

environment. The *in vivo* release rate of the system is therefore independent of its position in the GIT, because the membrane in the osmotic system is semi permeable in nature any polymer that is permeable to water but impermeable to solute (drug, organic and inorganic ions) can be selected example include cellulose ester such as cellulose acetate, cellulose diacetate, cellulose triacetate, cellulose propionate, and cellulose ether such as ethyl cellulose and Eudragit[35]. Among the cellulose polymer cellulose acetate membrane are mostly used because of its high water permeability characteristics and it can be adjusted varying the degree of acetylation of the polymer. The permeability of this membrane can be increased further by adding plasticizer to the polymer, which increases the water diffusion coefficient or hydrophilic fluxen hancer which increases the water sorption of the membrane. A few example of hydrophilic flux enhancer are Polyethylene glycols300, 400, 600, 1500, 4000, and 6000[36].

Ideal Property of Semi Permeable Membrane[22]

Semi Permeable Membrane must meet some performance criteria:

- ✓ 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.
- ✓ 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.

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 swellablepolymers[2]: 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[32]: Mixture of citric acid and sodium bicarbonate which creates pressures in the osmotic system and ultimately controls the release rate.
- ✓ Use of cyclodextrinderivatives[37]: 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.

Size of the Delivery Orifice[38]

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, CO2 laser beam (with output wavelength of 10.6µ) is used for drilling purpose, which offers excellent reliability characteristics at low costs.
- ✓ Indentation that is not covered during the coating process: Indentation is made in core tablets by using modified punches having needle on upper punch. This indentation is not covered during coating process which acts as a path for drug release in osmotic system.
- ✓ Use of leachable substances in the semipermeable coating: e.g. controlled porosity osmotic pump.

Use of Wicking Agent

The wicking agents are those agents which help to increase the contact surface area of the drug with the incoming aqueous fluid. The use of the wicking agent help to enhance the rate of drug released from the orifice of the drug. The examples are colloidal silicon dioxide, PVP & Sodium laryl sulphate[22].

Type and Amount of Plasticizer

In pharmaceutical industry coatings, plasticizers & low molecular weight diluents are added to modify the physical properties and improve film forming characteristic of polymers. The plasticizers can turn a hard and brittle polymer into a softer, more pliable material & make it more resistant to mechanical stress. The polymer can affect the permeability of the polymer films can result in the rate of change of drug release from the osmotic tablets[22].

Classification of Osmotic Pump

The OCODDS can be conveniently classified in to following types[39]:

Single Chamber Osmotic Pump

Elementary Osmotic Pump (EOP)[40-42]

Rose-Nelson pump was further simplified in the form of elementary osmotic pump, which made osmotic delivery as a major method of achieving controlled drug release. Elementary osmotic pump shown in Figure 1 was invented by Theeuwes in 1974[44,45]. EOP is the most basic device made up of a compressed tablet. The EOP consists of an osmotic core with the drug, surrounded by a semi permeable 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. The rate of imbibitions of water is determined by the fluid permeability of the membrane and the osmotic pressure of the compressed tablet. 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. Normally EOP deliver 60 – 80 % of its content at constant rate but it has short lag time of 30 – 60 minute. It is applicable formoderately soluble drug.

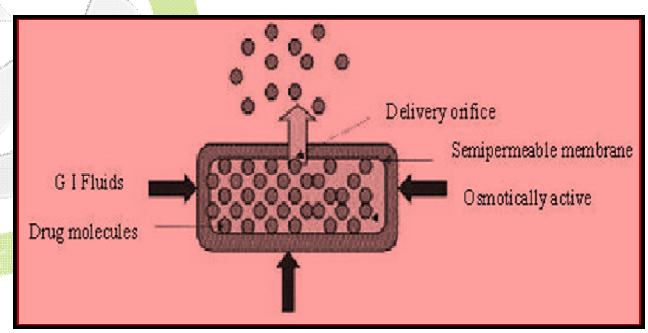

Figure 1: Elementary osmotic pump

Limitation

- ✓ SPM should be 200-300µm thick to withstand pressure
- ✓ Thick coatings lowers the water permeation rate
- ✓ Applicable mostly for water soluble drugs

Multi Chamber Osmotic Pump

Push Pull Osmotic Pump (PPOP)[43-45]

The two-layer push–pull osmotic tablet system appeared in 1980s. Push pull osmotic pump is a modified elementary osmotic pump through, which it is possible to deliver both poorly water-

soluble and highly water soluble drugs at a constant rate. The push–pull osmotic tablet consists of two layers, one containing the drug and the other an osmotic agent and expandable agent. A semipermeable membrane that regulates water influx into both layers surrounds the system. 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 nondrug layer simultaneously attracts water into that compartment, causing it to expand volumetrically, and the expansion of nondrug layer pushes the drug suspension out of the delivery orifice.

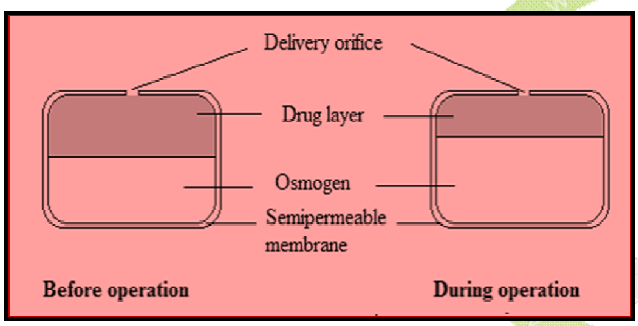

Figure 2: Push pull osmotic pump

Limitation

- ✓ Complicated laser drilling technology should be employed to drill the orifice next to the drug compartment.

Osmotic Pump With Non Expanding Second Chamber [46,47]

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 as at urated solution, irritation of GI tract is a risk. Example: The problem that leads 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.

Specific Types

Controlled porosity osmotic pump (CPOP) 45,4851

CPOP is an attempt to circumvent the need for a laser or mechanical drilled orifice. The CPOP contains water soluble additives (e.g., urea, nicotinamide, sorbitol, etc.) in coating membrane, which after coming in contact with water; dissolve resulting in an in-situ formation of a micro porous membrane. Then the resulting membrane is substantially permeable to both water and dissolved solutes and the mechanism of drug release from this system was found to be primarily osmotic, with simple diffusion playing a minor role. Drug release rate from CPOP depends on various factors like coating thickness, solubility of drug in tablet core, level of leachable pore-forming agent(s) and the osmotic pressure difference across the membrane. There are several obvious advantages inherent to the CPOP system. The stomach irritation problems are considerably reduced, as drug is released from the whole of the device surface rather from a single hole.

Further, no complicated laser-drilling unit is required because the holes are formed *in situ*.

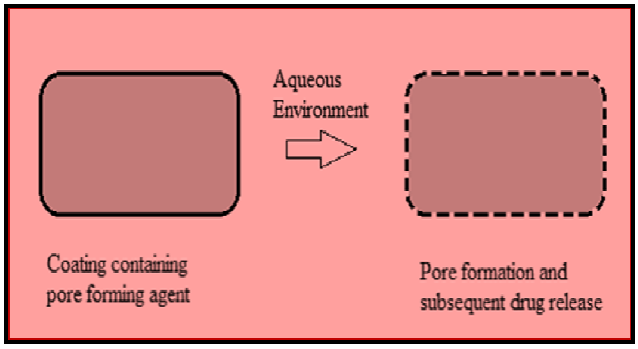

Figure 3: Controlled porosity osmotic pump

Limitation

- ✓ 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.

Monolithic Osmotic Systems[36]

It constitutes a simple dispersion of water-soluble a gentin polymer matrix. When the system comes in contact in with the aqueous environment water imbibitions 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 than 20 –30 volume per liter of the active agents is incorporated into the device as above this level, significant contribution from the simple leaching of the substance take place.

Osmotic Bursting Osmotic Pump[52]

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.

OROS – CT [53]

OROS-CT (Alza corporation) 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 semipermeable membrane. Incorporation of the cyclo dextrin-drug complex has also been used as an approach for delivery of poorly water soluble drugs from the osmotic systems. Ex. Sulfobutylether-β-cyclodextrin sodium salt serves as a solubilizer and osmotic agent.

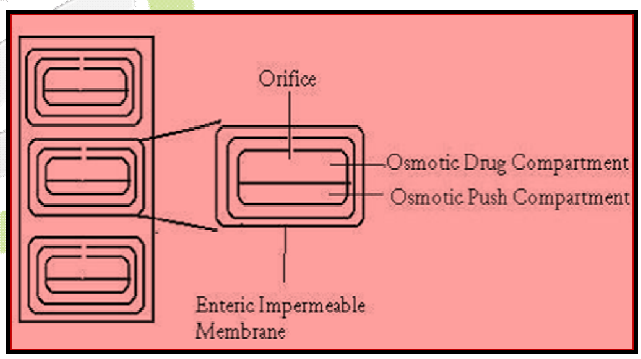

Figure 4: OROS – CT

Multi particulate Delayed Release Systems (MPDRS)[54]

MPDRS consist of pellets comprises of drug with or without osmotic agent, which are coated with a semipermeable membrane .When this system comes in contact with the aqueous environment, water penetrates in the core and forms a saturated solution of soluble component. The osmotic pressure difference results in rapid expansion of the membrane, leading to the formation of pores. The osmotic agent and the drug released through the pores according to zero order kinetics. The lag time

and dissolution rate were found to be dependent on the coating level and the osmotic properties of the dissolution medium.

Liquid Oral Osmotic System (L-OROS)[55,56]

Various LOROS systems available to provide controlled delivery of liquid drug formulations include L-OROS hardcap, L-OROS softcap, and a delayed liquid bolus delivery system. Each of these systems includes a liquid drug layer, an osmotic engine or push layer, and a semipermeable membrane coating. When the system is in contact with the aqueous environment, water permeates across the rate-controlling membrane and activates the osmotic layer. The expansion of the osmotic layer results in the development of hydrostatic pressure inside the system, there by forcing the liquid formulation to be delivered at the delivery orifice. Whereas L-OROS hardcap and L-OROS softcap systems are designed to provide continuous drug delivery, the L-OROS delayed liquid bolus 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 a rate-controlling semipermeable membrane (SPM). The delivery orifice is drilled on the placebo layer end of the capsule shaped device. When the osmotic engine expands, the placebo is released first, delaying release of the drug layer. Drug release can be delayed from 1 to 10 hours, depending on permeability of the rate-controlling membrane and the size of placebo.

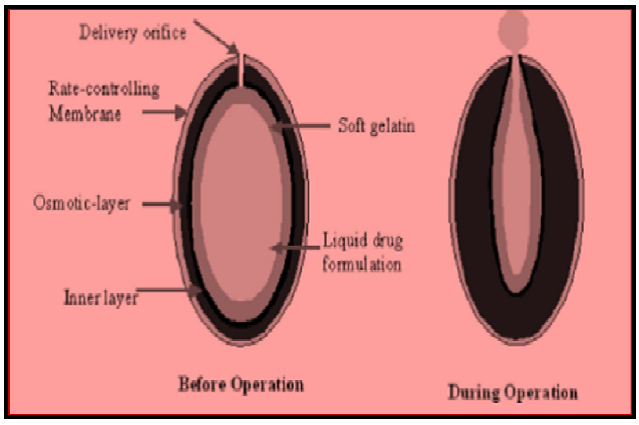

Figure 5: Liquid Oral Osmotic System

Recent Development

Sandwiched Osmotic Tablet (SOT)[49]

In this a tablet core 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 agent 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.

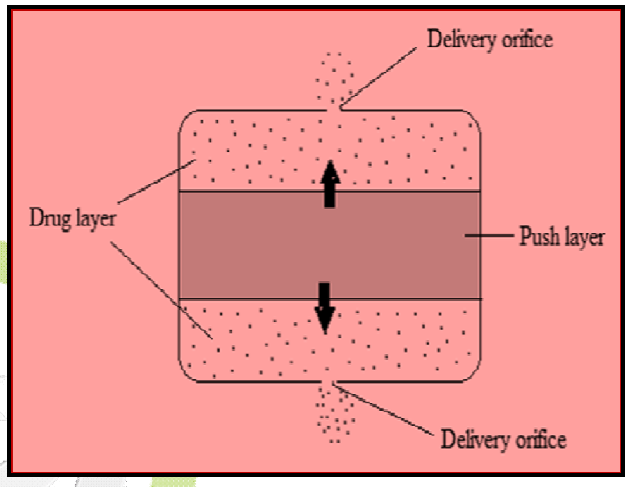

Figure 6: Sandwiched osmotic tablet

Osmat[57]

It is a novel osmotically driven matrix system, which utilizes the hydrophilic polymers to swell, and gel in aqueous medium forming a semipermeable 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 It is a novel osmotically driven matrix system, which utilizes the hydrophilic polymers to swell, and gel in aqueous medium forming a semipermeable 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.

Telescopic Capsule for Delayed Release[58,59]

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.

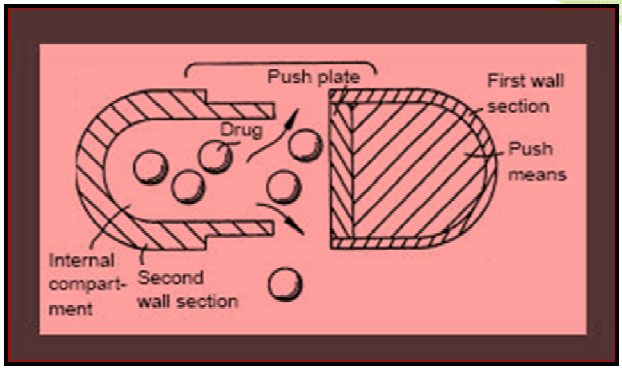

Figure 7: Telescopic Capsule for Delayed Release

Longitudinally Compressed Tablet (LCT) Multilayer Formulation[60]

The LCT multilayer formulation is the advanced design. As with the push-pull system it consists of an osmotic push layer and can be configured to contain several drug layers. The opinion of multiple drug layers provides increased flexibility and control over the pattern of release of medication from the system, as opposed to the single layer used in the push-pull system, which can deliver a drug only in a zero order fashion. For example, two drug layers could be formulated with different drug concentration to provide modulation in the release rate profile. As with the push-pull formulation, water is absorbed through the exposed semipermeable tablet shell, expanding the push compartment and releasing the drug primarily through the first compartment through the laser drilled orifice at a predetermined controlled rate. After most of the drug release begins from the second compartment at a different rate. Varying the relative viscosity and hydrophilicity of the drug layer components can control the amount of mixing between the multiple drug layers. This allows even greater flexibility to achieve the target release profile.

The LCT multilayer formulation can also be formulated with different drugs in different layers to provide combination therapy. Similar to the push-pull system, drug delivery by the LCT multilayer formulation can be unaffected by gastric pH, gut motility and the presence of food, depending on where in the GI tract the drug is released.

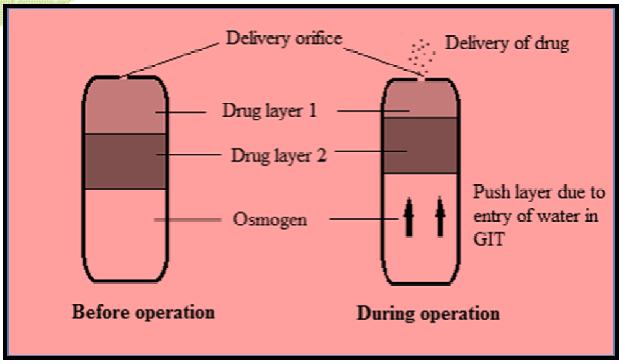

Figure 8: Multilayer osmotic pump

Lipid Osmotic Pump[61]

Merk describes an osmotic pump for the lipid delivery as shown in the figure. The device concerns an osmotic agent for dispensing beneficial active agent that has poor solubility in water. The core of the system comprises a beneficial amount of a sustantially water-

insoluble active agent, which is lipid soluble or lipid- wettable; a sufficient amount of water insoluble lipid carrier, which is liquid at the temperature of use to dissolve or suspend the drug and agent to ensure the release of the lipid carrier of the drug from the pump. The water insoluble wall is microporous and is wetted by lipid carrier. The device is prepared by first dissolving the drug of interest in the lipid vehicle. The osmogent (Sodium chloride) is dispersed in the melted lipid and then quenched-cool to form a lump that are broken and made into tablet. The microporous is coated at a moderate flow of unheated ambient air.

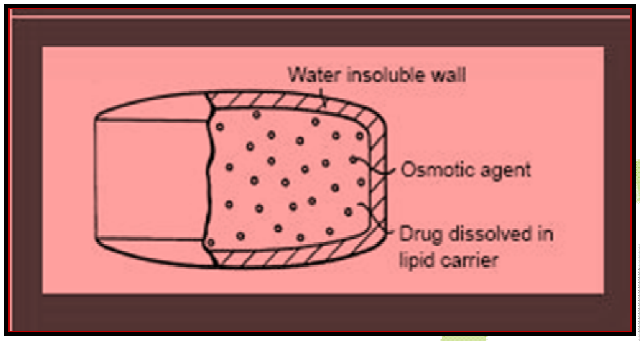

Figure 9: Lipid osmotic pump

Pulsatile Delivery System[46]

Pulsatile systems are gaining a lot of interest as they deliver the drug at the right site of action at the right time and in the right amount, thus providing spatial and temporal delivery and increasing patient compliance. These systems are designed according to the circadian rhythm of the body. The principle rationale for the use of pulsatile release is for the drugs where a constant drug release, i.e., a zero order release is not desired. The release of the drug as a pulse after a lag time has to be designed in such a way that a complete and rapid drug release follows the lag time. This type of tablet system consist of core coated with two layer of swelling and rupturable coatings herein they used spray dried lactose and microcrystalline cellulose in drug core and then core was coated with swelling polymer croscarmellose sodium and an outer rupturable layer of ethyl cellulose. Pulsatile systems can be classified into single and multiple-unit systems. Single-unit systems are formulated either as capsule-based or osmosis based systems. Single-unit systems are designed by coating the system either with eroding/soluble orrupturable coating. In multiple-unit systems, however, the pulsatile release is induced by changing membrane permeability or by coating with a rupturable membrane.

Miscellaneous Devices[27]

Patent 6352721 (2002) assigned to Osmotica Corporation(Tortola, British Virgin Islands) report a combined diffusion osmotic pump drug delivery system . The device has a centrally located expandable core that is completely surrounded by active substances- containing layer, which is completely surrounded by a membrane. The core consist of an expandable hydrophilic polymer and an optional osmogen (Kaushal et al, 2003).The composition is completely surrounding the core comprises an active substances, an osmogent and an osmo polymer. The membrane is micro porous in nature and may have a delivery orifice. The device is capable of delivering insoluble, slightly soluble, sparingly soluble and very soluble drug to the environment.

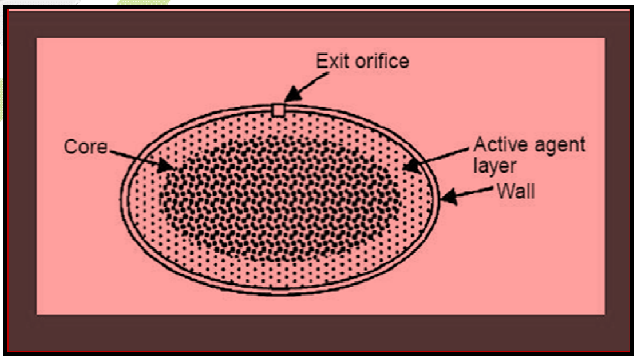

Figure 10: Miscellaneous devices

Evaluation of Osmotic Controlled Drug Delivery System

Oral osmotic drug delivery systems can be evaluated using a range of studies [62]:

Visual Inspection

Visual inspection of the film can be done for smoothness, uniformity of coating, edge coverage and luster.

Coating Uniformity

The uniformity of coating among the tablets can be estimated by determining the weight, thickness and diameter of the tablet before and after the coating.

Coat Weight and Thickness

The coat weight and thickness can be determined from depleted devices following careful washing and drying of the film, using standard analytical balance and screw gauge, respectively.

Orifice Diameter

The mean orifice diameter of osmotic pump tablet can be determined microscopically using pre calibrated ocular micrometer.

In vitro Drug Release

The in vitro delivery rate of drugs from osmotic systems can be determined using diverse methodologies, including vertically reciprocating shaker, conventional USP dissolution apparatus I and II, flow-through apparatus, etc.

Marketed Products

In Vivo Evaluation

As the environment in the intestinal tract of the dog is quite similar to that of the human beings in terms of pH and motility, dogs have widely been used for in vivo delivery rate measurement of drug(s) from oral osmotic drug delivery systems and also to establish *in vitro /in vivo* correlation (*IVIVC*). In vivo evaluation can also be performed in healthy human volunteers. Various pharmacokinetic parameters (Cmax, Tmax, AUC and MRT) and relative bioavailability are calculated.

CONCLUSION

Development efforts of oral osmotic controlled drug delivery systems during recent years have been very dynamic with the emergence of new technologies and products. With the expiration of the oral osmotic controlled drug delivery systems primary patents and the increasing demand of health authorities for improved patient treatment compliance and tolerability, the oral osmotic controlled drug delivery systems S is primed to increase their market within oral modified-release dosage forms.

Table 2: Examples of some marketed band of Osmotic drug delivery system

Product name	Chemical name	Type of delivery	Developer / Marketer
Acutrim	Phenylpropanolamine	Elementary pump	Alza/Heritage
Alpress LP	Prazosin	Push -Pull	Alza/Pfizer
CalanSR	Verapamil	Push -Pull	Alza/Pfizer
Concerta	Methyl phenidate	Push -Pull	Alza
Ditropan XL	Oxybutinin chloride	Push -Pull	Alza/UCB Pharma
Efidac 24	Pseudoephiderine	Elementary pump	Aza/Novartis
Glucotrol XL	Glipizide	Push -Pull	Alza/Pfizer
MinipressXL	Prazosine	Push -Pull	Alza/Pfizer
ProcadiaXL	Nifedipine	Push -Pull	Alza/Pfizer
Tiamate	Diltiazem	Elementary pump	Merck/Aventis
Volmax	Albuterol	Push -Pull	Alza/Muro Pharmaceuticals

Developed as a drug delivery platform for delivering drugs regardless of their physico-chemical properties, oral osmotic controlled drug delivery systems have several applications (i) in early clinical phases (including early-stage exploration of pharmacokinetics), (ii) in novel dosage form development and (iii) in product life-cycle management. The clinical benefits of oral osmotic controlled drug delivery systems 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. Nowadays, the large variety of oral osmotic controlled drug delivery systems technologies available allows an interesting adaptation of the system to the drug properties and dosage strength. 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.

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