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Review Article

A REVIEW ON ORAL OSMOTICALLY DRIVEN SYSTEMS

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ABSTRACT

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 controlled release (CR) system is most acceptable dosage form by the patients. Drugs having short biological half-life and poor water solubility are the suitable candidate for development of CR system. Research revealed that conventional matrix or reservoir type formulations exhibits bioavailability issues due to gastric pH variations and is also affected by the hydrodynamic conditions of the body. Introduction of Osmotically controlled oral drug delivery systems (OCDDS) overcame these issues. OCDDS utilize osmotic pressure for controlled delivery of active agent(s). Drug delivery from these systems is independent of the physiological factors of the gastrointestinal tract and these systems can be utilized for systemic as well as targeted delivery of drugs. 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. This review brings out new technologies, fabrication and recent clinical research in osmotic drug delivery.

KEY WORDS: Osmosis, Osmotic pumps, Osmotic agent, Zero-order, Semipermeable membrane.

INTRODUCTION

Oral ingestion is one of the oldest and most extensively used routes of drug administration, providing a convenient method of effectively achieving both local and systemic effects. Novel drug delivery systems (NDDS) are the key area of pharmaceutical research and development. The reason is relatively low development cost and time required for introducing a NDDS as compared to new chemical entity. The various NDDS available in market, as an oral controlled release [CR] system that grip the major market share because of their understandable advantages of easiness of administration and better patient compliance.CR delivery system offer desired concentrations of drug at the absorption site allow maintenance of plasma concentrations in the therapeutic range and reducing the dosing frequency. Majority of oral CR dosage forms drop in the class of reservoir, matrix, or osmotic system. In matrix systems, the drug is mixed in a polymer matrix and the drug release take place by partition of drug in to the polymer matrix and release medium. In difference, reservoir

system has a drug center surrounded or coated by a rate controlling membrane. Though, factors like presence of food, pH, and other physiological factors may influence drug release from conventional CR systems [matrix and reservoir] (Syed *et al.*2015).

Osmotically controlled drug delivery systems (OCDDS) is one of the most promising drug delivery technologies that use osmotic pressure as a driving force for controlled delivery of active agents. Drug release from OCDDS is independent of pH and hydrodynamic conditions of the body because of the Semipermeable nature of the rate-controlling membrane and the design of deliver orifice used in osmotic systems, so a high degree of *in vitro/in vivo* correlation is achieved. It is also possible to obtain higher release rates through these systems than through other diffusion-based systems. There are over 240 patented osmotic drug delivery systems. They are also known as GITS (gastro-intestinal therapeutic system) and today, different types of osmotic pumps, of various drugs, are available in the market to fulfil patient's need and requirement. This review mainly focuses on the theoretical aspects, basic components of OCDDS, factors affecting OCDDS, different technologies, marketed products and future aspects of OCDDS (Patel *et al.* 2013).

HISTORIC BACK GROUND

The Rose Nelson pump

In 1955 two Australian physiologist Rose and Nelson reported the first osmotic pump. They were interested in delivery of drugs to the gut of sheep and cattle**.** (Vyas *et al*. 2001)

- A drug chamber with an orifice.
- A salt chamber with elastic diaphragm containing excess solid salt.
- A water chamber.

The drug and water chamber are separated by a rigid semi permeable membrane. The difference in osmotic pressure across the membrane moves water from the water chamber into salt chamber. The volume of the salt chamber increases because of this water flow, which distends the latex diaphragm separating salt and drug chamber there by pumping drug out of this device. The pumping rate of Rose-Nelson pump is given by the equation: (Rose and Nelson 1955).

dm/dt = dv/dt *c ---------- (1)

Where:

dm/dt = Drug release rate.

dv/dt = Volume flow of water into salt chamber.

c = Concentration of drug into drug chamber.

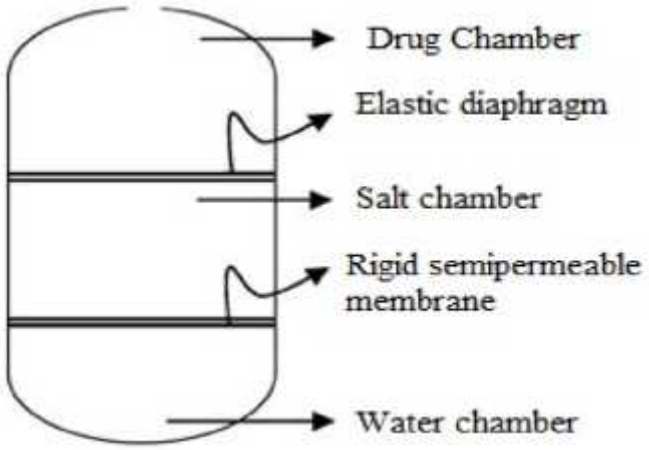

Figure 1: Rose Nelson pump

Higuchi Leeper pump

The design of Higuchi Leeper pump represents the first simplified version of the Rose Nelson pump made by the Alza Corporation in the early 1970. The benefit of this pump over Rose Nelson pump is that it does not have water chamber and the device is activated by water imbibed from the surrounding environment. This means the pump is first prepared and then loaded with the drug and then store for weeks or months prior to use (Higuchi and Leeper 1973).

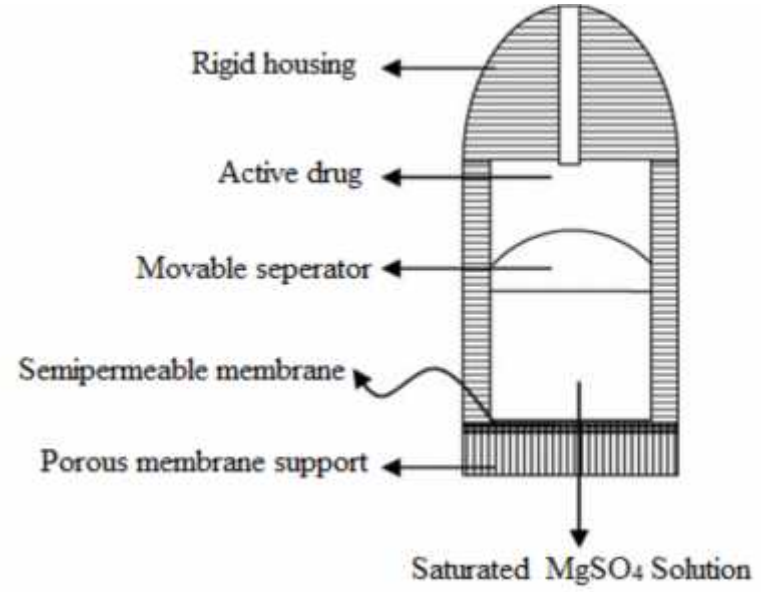

Figure 2: Higuchi Leeper pump

Higuchi- Theeuwes pump

In the early 1970 Higuchi – Theeuwes developed a similar form of Rose Nelson pump. The semi permeable wall itself act as a rigid outer casing of the pump. The device is loaded with drug prior to use (Vyas et al, 2001). When the device is put in an aqueous environment the release of the drug follows a time course set by the salt used in the salt chamber and the permeability of the outer membrane casing (Theeuwes 1975).

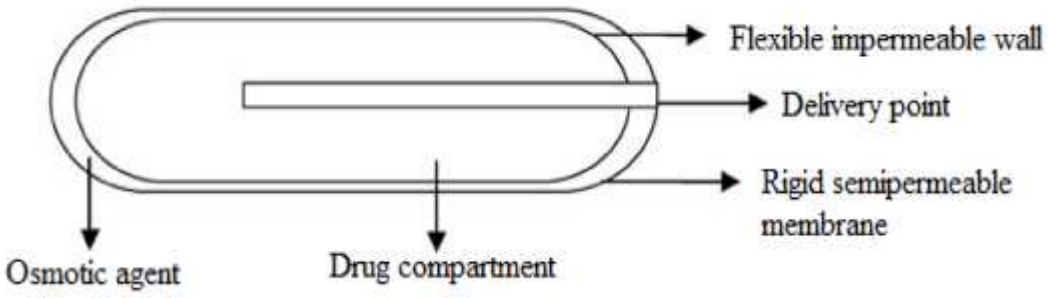

Figure 3: Higuchi- Theeuwes pump

Advantages

The following advantages have contributed to the popularity of osmotic drug delivery systems

- The delivery rate of zero order is achievable with osmotic system.
- Delivery may be delayed or pulsed, if desired.

- Higher release rates are possible with osmotic system compared with conventional diffusion-controlled delivery system.
- The release rate of osmotic system is highly predictable.
- For oral osmotic system, drug release is independent to gastric pH and hydrodynamic condition.
- The release from osmotic system is minimally affected by presence of food in gastrointestinal tract.
- A high degree of *in vivo-in vitro* correlation is obtained in osmotic system.
- Improve patient compliance with reduced frequency (Gupta *et al.*2014).

Disadvantages of ODDS

- Subjected to dose dumping if membrane breaks.
- Somewhat more expensive to formulate than coating tablets.
- Possible hole plugging (Sancheti *et al.*2014).

BASIC CONCEPTS

Principle of Osmosis

Osmosis can be defined as the spontaneous movement of a solvent from a solution of lower solute concentration to a solution of higher solute concentration through an ideal Semipermeable membrane, which is permeable only to the solvent but impermeable to the solute. The pressure applied to the higher-concentration side to inhibit solvent flow is called the osmotic pressure (Thummar *et al.* 2013).

Drug

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 (Nikam *et al.*2012).

Basic Criterion for Drug Selection:

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

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 build-up 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. (Singla *et al.*2012)

Semipermeable Membrane

An important part of the osmotic drug delivery system is the Semipermeable membrane housing. Therefore, the polymeric membrane selection is important to the osmotic delivery formulation. The membrane should possess certain characteristics, 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 (Ade *et al.*2013).

Hydrophilic and Hydrophobic Polymers

These polymers are used in the formulation development of osmotic systems for making drug containing matrix core. 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 (Gupta *et al.*2001). Ionic hydrogels such as sodium carboxymethyl cellulose are preferably used because of their osmogenic nature

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. 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. The examples are colloidal silicon dioxide, PVP and Sodium lauryl sulfate. (Patel *et al.* 2013)

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. Non swellable solubilizing agents are classified into three groups, (Patel *et al.* 2013)

(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 non-ionic surfactants (e.g.,

Tween 20, 60, and 80, polyoxy ethylene or polyethylene 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 (Ade *et al.*2013).

Coating Solvents

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, ethyl acetate, 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. (Gupta *et al.*2001)

Plasticizers

In pharmaceutical coatings, plasticizers, or low molecular weight diluents are added to modify the physical properties and improve film forming characteristics of polymers. Plasticizers can change visco elastic behaviour of polymers significantly. Plasticizers can turn a hard and brittle polymer into a softer, more pliable material, and possibly make it more resistant to mechanical stress. 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. (Singla *et al.*2012)

Pore forming agents

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 pores forming agents cause the formation of microporous membrane. The microporous 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 (Gupta *et al.*2001). Pores may also be formed in the wall by the volatilization of components in a polymer solution or by chemical reactions in a polymer solution which evolves gases prior to application or during application of solution to the core mass resulting in the creation of polymer foams serving as the porous wall. The pore-formers should be non-toxic, and on their removal, channels should be formed. The channels become a transport path for fluid (Vyas *et al.*2001).

Flux regulating agents

Delivery systems can be formulated to regulate the permeability of the fluid by incorporating flux-regulating agents in the layer. Hydrophilic substances improve the flux, whereas hydrophobic materials tend to decrease the flux. Insoluble salts or insoluble oxides, which are substantially water-impermeable materials, also can be used for this purpose (Ade *et al.*2013).

FACTORS INFLUENCING THE DESIGN OF OSMOTIC CONTROLLED DRUG DELIVERY SYSTEMS

Drug Solubility

For the osmotic system, solubility of drug is one of the most important parameters affecting drug release kinetics from osmotic pumps. The kinetics of osmotic drug release is directly related to the drug solubility within the drug core. Assuming a tablet core of pure drug, the fraction of core released with zero-order kinetics is given by equation.

$$F(z) = 1 - S/\rho \quad \text{..... (2)}$$

Where, F (z) is the fraction released by zero-order kinetics, S is the drug's solubility (g/cm^3), and ρ is the density (g/cm^3) of the core tablet. Drugs with a density of unity and the solubility of ≤ 0.05 g/cm^3 would be released with ≥ 95% zero-order kinetics, according to Eq. (2). At the same time, highly water-soluble drugs would demonstrate a high release rate that would be zero-order for a small percentage of the initial drug load. Thus, the intrinsic water solubility of many drugs might prohibit them from incorporation into an osmotic pump. Candidate drugs for osmotic delivery have water solubility in the range 50–300 mg/ml. Some of the approaches that have been used to modulate drug solubility within the core include

- Co-compression of the drug with excipients, which modulate the drug's solubility within the core

- Use of effervescent mixtures to speed up the release of poorly soluble drug from the orifice
- Use of various cyclodextrin,is derivatives to solubilise poorly water soluble drug
- Use of alternative salt form that has optimum water solubility
- Use of encapsulated excipients
- Use of lyotropic crystals
- Use of wicking agents (Patel *et al.* 2013)

Delivery orifice

Majority of osmotic delivery systems contain at least one delivery orifice (preformed or formed in situ) in the membrane for drug release. Size of delivery orifice must be optimized to control the drug release from osmotic system. The size of the delivery orifice must be smaller than a maximum size S_{max} to minimize drug delivery by diffusion through the orifice. Furthermore, the area must be sufficiently large, above a minimum size S_{min}, to minimize hydrostatic pressure build-up in the system. Otherwise, the hydrostatic pressure can destroy 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. Methods to create a delivery orifice in the osmotic tablet coating are:

- Mechanical drill
- Laser drill: This technology is well established for producing sub-millimetre size hole in tablets. Normally, CO_2 laser beam (with output wavelength of 10.6µ) is used for drilling purpose, which offers excellent reliability characteristics at low costs.
- Indentation that is not covered during the coating process: Indentation is made in core tablets by using modified punches having needle on upper punch. This indentation is not covered during coating process which acts as a path for drug release in osmotic system.
- Use of leachable substances in the Semipermeable coating: e.g. controlled porosity osmotic pump (Thummar *et al.*2013).

CLASSIFICATION OF OSMOTIC DRUG DELIVERY SYSTEMS

The OCODDS can be conveniently classified in to following types:

Single chamber osmotic pump

- Elementary osmotic pump

Multi chamber osmotic pump

- Push pull osmotic pump.
- Osmotic pump with non-expanding second chamber.

Specific types

- Controlled porosity osmotic pump.
- Monolithic osmotic systems.
- Osmotic bursting osmotic pump.
- OROS – CT
- Multi particulate delayed release systems (MPDRS)
- Liquid Oral Osmotic System. (L-OROS)

Recent Development

- Sandwiched Osmotic Tablet (SOT)
- Longitudinally Compressed Tablet (LCT) Multilayer Formulation
- Telescopic Capsule for Delayed Release
- Lipid Osmotic Pump
- Pulsatile Delivery System (Syed *et al.* 2015)

Single Chamber Osmotic Pump

Elementary Osmotic Pump (EOP)

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 was invented by Theeuwes in 1974 The EOP consist of single layered tablet core containing a water-soluble drug with or without another osmotic agent. A semi permeable membrane surrounds the tablet core. When such a system is swallowed water from the GIT enter through the membrane in the core, the drug dissolved and the drug solution is pumped out through the exit orifice. This process continues at a constant rate until the entire solid drug inside the tablet has been dissolved drug continues to be delivered but at a declining rate until the osmotic pressure between outside environment and saturated drug solution. Normally the EOP delivers 60 - 80% of its content at a constant rate and there is a short lag time of 30- 60 min as the system hydrates before zero order drug release from the EOP is obtained.

Limitation

- SPM should be 200-300µm thick to withstand pressure
- Thick coatings lowers the water permeation rate
- Applicable mostly for water soluble drugs (Ade *et al.* 2013)

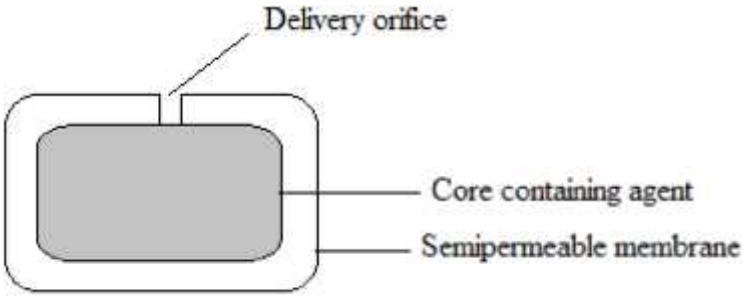

Figure 4: Elementary osmotic pump

Multi Chamber Osmotic Pump

Push Pull Osmotic Pump (PPOP)

The PPOP, which was developed by Alza Corporation, consists of two compartments separated by an elastic diaphragm (optional). 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. (Thummar *et al.* 2013)

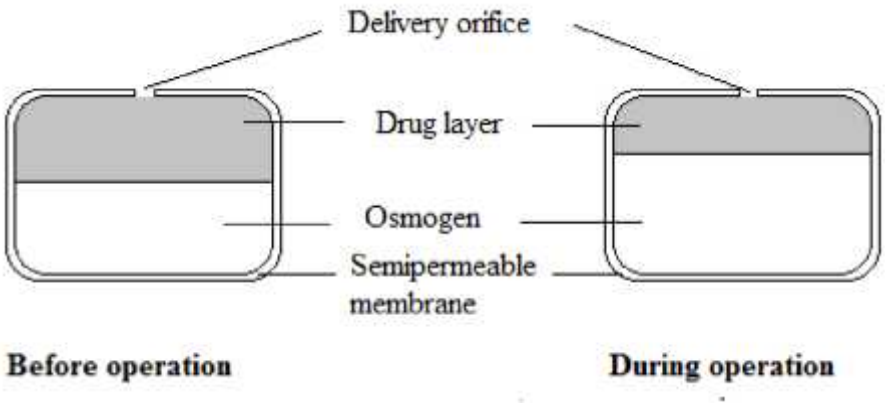

Figure 5: Push pull osmotic pump

Limitation

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

Osmotic Pump with Non-Expanding Second Chamber

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 rated solution, irritation of GI tract is a risk. Example: The problem that leads to withdrawal of osmosis, 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 consists 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. (Patel *et al.*2012) 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)

A controlled porosity osmotic pump-based drug delivery system Unlike the elementary osmotic pump (EOP) which consists of an osmotic core with the drug surrounded by a Semipermeable membrane drilled with a delivery orifice, controlled porosity of the membrane is accomplished by the use of different channelling agents in the coating7. The CPOP contains water soluble additives in coating membrane, which after coming in contact with water; dissolve resulting in an in-situ formation of a microporous membrane. Then the resulting membrane is substantially permeable to both water and dissolved solutes and the mechanism of drug release from these systems was found to be primarily osmotic, with simple diffusion playing a minor role. Drug delivery from asymmetric membrane capsule is principally controlled by the osmotic pressure of the core formation. In-situ formed delivery orifice in the asymmetric membrane in mainly responsible for the solubilisation in the core for a drug with poor water solubility. (Gupta *et al.*2001)

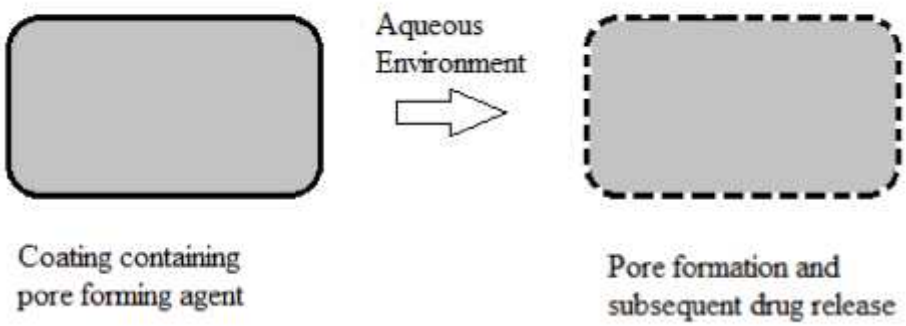

Figure 6. Controlled porosity osmotic pump

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

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 (Gupta *et al.*2001). However, this system fails if more than 20 –30 volume per litre 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

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 (Thorat *et al.* 2012).

OROS – CT

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 semi permeable membrane. Incorporation of the cyclodextrin-drug complex has also been used as an approach for delivery of poorly water soluble drugs from the osmotic systems. Ex. Sulfobutylether-Bcyclodextrin sodium salt serves as a solubilizer and osmotic agent (Parashar *et al*.2012).

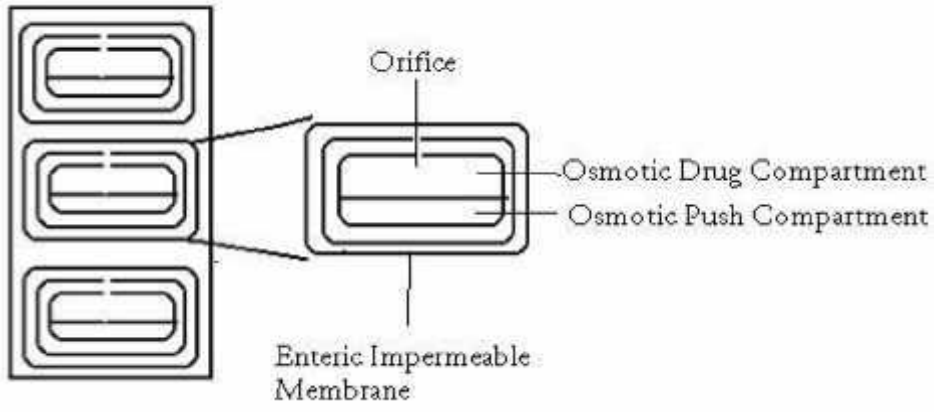

Figure 7: OROS – CT

Multi particulate Delayed Release Systems (MPDRS)

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. (Khatri *et al.* 2016)

Liquid Oral Osmotic System (L-OROS)

Various LOROS systems available to provide controlled delivery of liquid drug formulations

Include L-OROS hard cap, L-OROS soft cap, 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, thereby forcing the liquid formulation to be delivered at the delivery orifice. Whereas L-OROS hard cap and L-OROS soft cap 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. (Khatri *et al*. 2016)

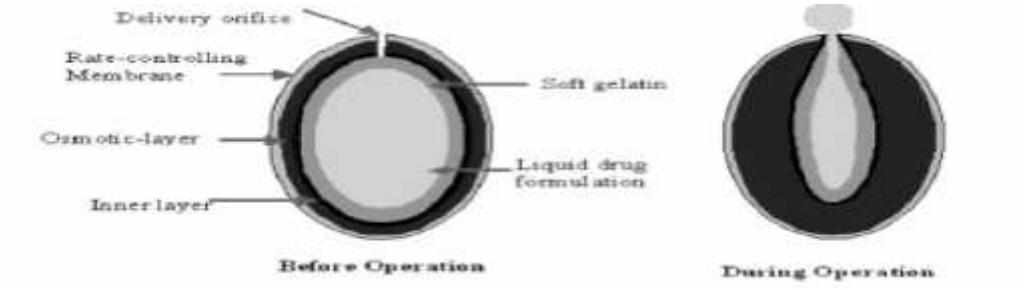

Figure 8: Liquid Oral Osmotic System

Recent Development

Sandwiched Osmotic Tablet (SOT)

It is composed of polymeric push layer sandwiched between two drug layers with two delivery orifices. When placed in the aqueous environment the middle push layer containing the swelling agents' swells and the drug is released from the two orifices situated on opposite sides of the tablet and thus SOTS can be suitable for drugs prone to cause local irritation of the gastric mucosa (Ghosh *et al.*2011).

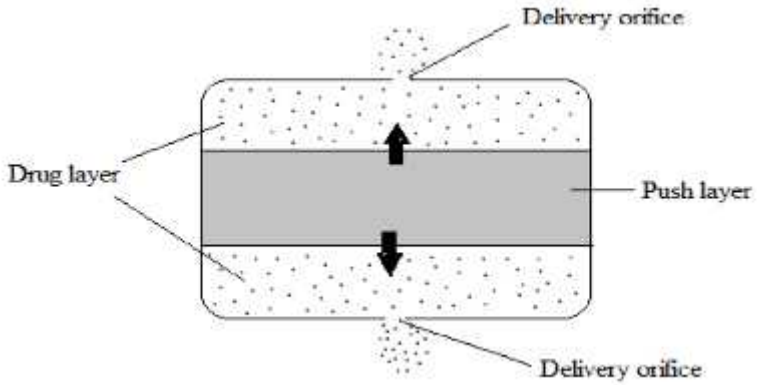

Figure 9: Sandwiched osmotic tablets

Longitudinally Compressed Tablet (LCT) Multilayer Formulation

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 **(**Gupta *et al.* (2014).

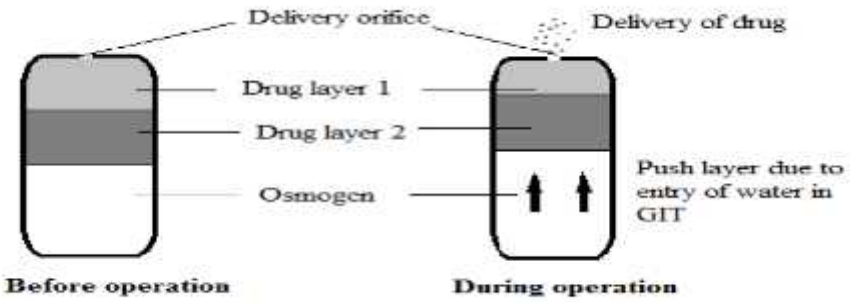

Figure 10: Multilayer osmotic pump

Telescopic Capsule for Delayed Release

This device consists of two chambers, the first contains the drug and an exit port, and the second contains an osmotic engine. A layer of wax like material separates the two section. To assemble the delivery device, the desired active agent is placed into one of the sections by manual or automated fill mechanism. The bilayer tablet with the osmotic engine is placed into a completed cap part of the capsule with the convex osmotic layer pointed in to the closed end of the cap and the barrier into the closed end of the cap and the barrier layer exposed towards the cap opening. The open end of the filled vessel is fitted inside the open end of the cap, and the two pieces are compressed together until the cap, osmotic bilayer tablet and vessel fit together tightly. As fluid is imbibed the housing of the dispensing device, the osmotic engine expands 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. (Prajapati *et al.*2012)

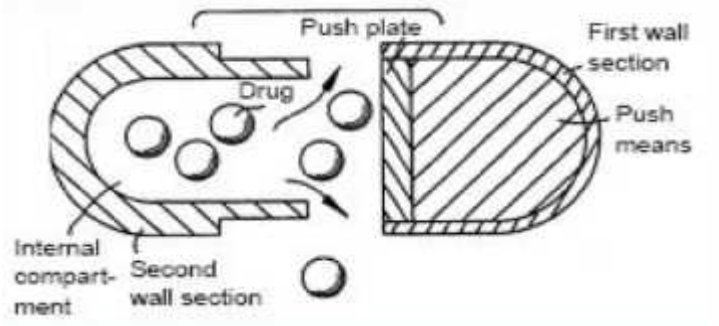

Figure 11: Telescopic Capsule for Delayed Release

Lipid Osmotic Pump

Merk describes an osmotic pump for the lipid delivery. 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 (Ghosh *et al.*2011).

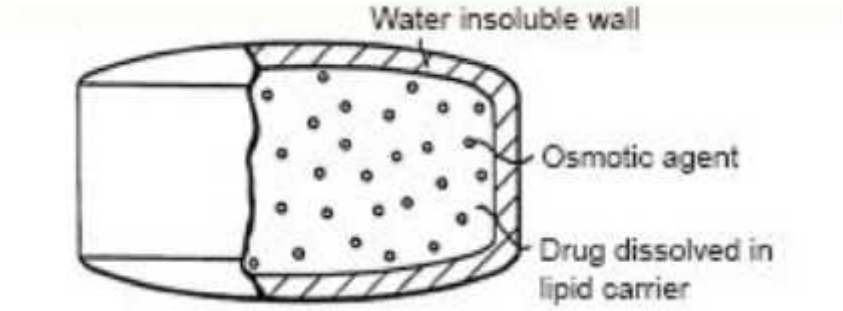

Figure 12: Lipid osmotic pump

Pulsatile Delivery System

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 consists 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 or rupturable coating. In multiple-unit systems, however, the pulsatile release is induced by changing membrane permeability or by coating with a rupturable membrane. (Prajapati *et al.*2012)

EVALUATION OF OSMOTIC CONTROLLED DRUG DELIVERY SYSTEM

Oral osmotic drug delivery systems can be evaluated for following**:**

- **Visual inspection**: Visual inspection of the film for smoothness, uniformity of coating, edge coverage and lustre.
- **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
- **Effect of pH: An** Osmotically controlled release system delivers its contents independently of external variables. To check this, dissolution media with different pH is used.
- **Effect of agitation intensity:** In order to study the effect of agitational intensity of the release media, release studies is carried out in dissolution apparatus at various rotational speeds. (Vishwakarma *et al.*2011)

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 been widely 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 (C_{max}, T_{max}, AUC and MRT) and relative bioavailability are calculated (Mane *et al.*2012).

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 is primed to increase their market within oral modified-release dosage forms.

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