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COMPREHENSIVE REVIEW ON OSMOTIC DRUG DELIVERY SYSTEM

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ABSTRACT

Uncontrolled immediate drug release may sometimes cause local gastro intestinal or systemic toxicity, require frequent administration due to shorter half-life. Further, the rate and extent of absorption of drug from conventional dosage forms may vary greatly depending on factors such as presence of excipients, physicochemical properties of the drug, various physiological factors such as presence or absence of food, pH of gastro intestinal tract, gastro intestinal motility and so on. Scientist continuous efforts lead to development of new drug delivery system (NDDS) and currently it is essential area for drug research and development. The reason is the low cost of development and shorter time required to launch the NDDS compared to the new chemical molecule development. Through the NDDS, the existing drug molecule can gain a 'new life,' thus, increasing its market value, competitiveness, and patent life. Among the various NDDS available in the market, oral controlling (CR) systems hold the largest market share due to their obvious benefits for easier management and better patient compliance. The critical milestone in the oral NDDS development exist when the Osmotic drug delivery system (ODDS) was discovered, a new and highly versatile system, because drug release from these systems is independent of pH and other body parameters on a large scale and it is possible to quantify the release characteristics by improving drug properties and system. This review paper highlight the fabrication of ODDS, various novel osmotic technology, various factor contributing impact on drug release from ODDS,status of currently marketed as well as under development product based on ODDS.

KEYWORD: Osmotic Drug Delivery System, Osmosis, controlled release, osmotic pressure, novel drug delivery system.

1.0 INTRODUCTION

The oral route remains one of the 'preferred' routes of drug administration and has seen significant success over the past few decades in improving the oral delivery of drug molecules. Oral administration is one of the oldest and most widely used drug administration route, providing an easy way to effectively achieve local and systemic effects.[1, 42]

The complete action of a drug molecule depends on its therapeutic function and the efficiency brought to the aid site. Increased awareness of the latter has led to the emergence and development of new drug delivery systems (NDDS), which are aimed at improving the performance of potential drug molecules. The new drug delivery programs (NDDS) are an important area for drug research and development. The reason is the low cost of development and the time required to launch the NDDS ($ 20-50 million and 3 - 4 years, respectively) compared to the new chemical molecule (about $ 500 million and 10 - 12 years, respectively).[2] Focus on the NDDS includes the novel designing of NDDS of new drugs on the one hand and the other NDDS of established drugs to improve trade value. Through the NDDS, the existing drug molecule can gain a 'new life,' thus, increasing its market value, competitiveness, and patent life. Among the various NDDS available in the market, oral controlling (CR) systems hold the largest market share due to their obvious benefits for easier management and better patient compliance.

Treatment for serious illness or chronic illness is achieved through the delivery of medicines to patients for many years. These drug delivery systems include pills, not to mention, suspensions, creams, ointments, liquids and aerosols. Today these standard drug delivery systems are widely used. The term drug delivery can be defined as a technique used to obtain medical substances within the human body. Conventional drug treatment requires periodic dose of drug at very small interval time. These agents are designed to produce high stability, efficacy and high bioavailability. In most drugs, conventional drug administration methods work, but some drugs are less stable or toxic and have fewer treatment options. Some drugs have solubility problems. In such cases, a method of continuous ingestion of the therapeutic agent is required to maintain desired plasma levels as shown in Figure 1.[3]

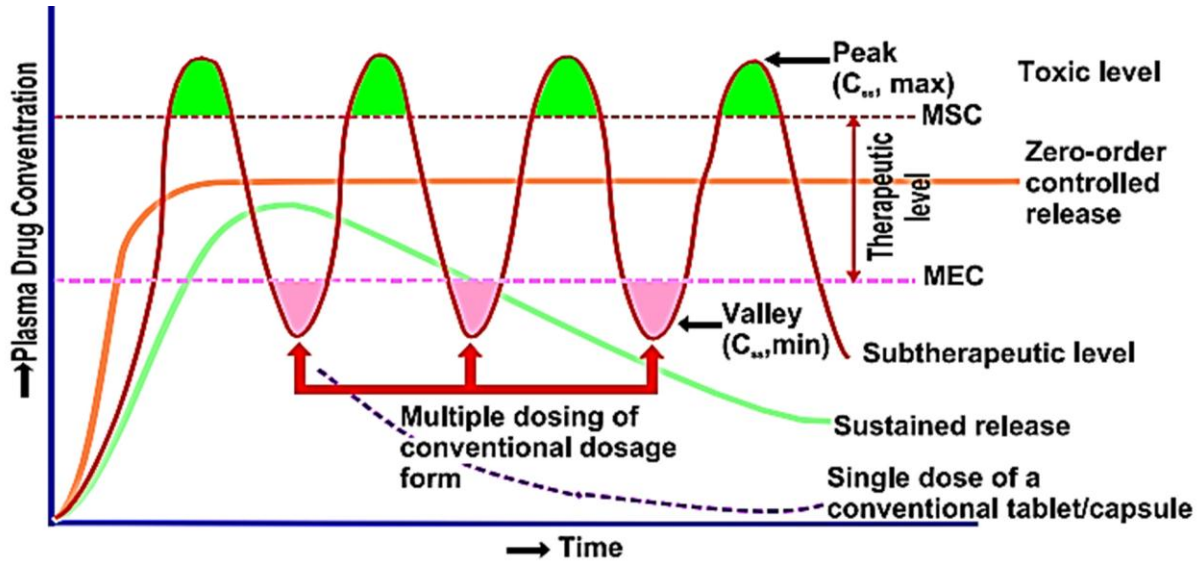


Figure 1: Plasma drug concentration profiles for conventional multiple dosing Vs single dose of Zero order controlled release or sustained release dosage form.[3]

To address these issues, controlled drug programs were introduced over the past three decades. These delivery systems have many advantages over conventional drug delivery systems (Table 1). The main purpose of controlled drug delivery systems is to improve the effectiveness of drug treatment methods. With controlled drug delivery systems, the oral administration route has received much attention, this is because there is more flexibility in the formulation of the oral form than in the parental formulation. The most oral controlled release systems rely on the diffusion, dissolution or combination of both methods, to produce slow release of the drug into the intestinal tract.[42]

CR delivery systems provide the desired concentration of the drug at the absorption zone allowing for the retention of plasma concentrations within the treatment range and reducing the frequencyof dosage. These products often offer significant benefits over IR dosage form, including greater efficacy in treating chronic conditions, reduced side effects, and ease of use for patients due to a simplified dosage schedule.

Table 1: Advantages of controlled release dosage forms over conventional forms.	
Advantage	**Explanation**
Reduction in drug blood levelfluctuation.	By controlling the rate of drug release, "peaks and valleys" of drug blood levels are eliminated.
Frequency reduction indosing.	Extended release products deliver frequently more than a single dose of medication and thus they may be taken less often thanconventional forms.
Enhanced patientsconvenience and compliance.	With less frequency of dose administration, a patient is less apart to neglect taking a dose. There is also greater patient and/or caregiver convenience with dynamic and night time medication administration.
Reduction inadverse side effects.	Because there are fewer drug blood level peaks outside of the drug's therapeutic range and into the toxic range, adverse side effects occur less frequently.
Reduction in overall health carecosts.	Although the initial cost of extended-release dosage forms may be greater than that for conventional dosage forms, the overall cost of treatment may be less due to enhanced therapeutic benefit, fewer side effects, and reduced time required of health care personnel to dispense and administer drugs and monitor patients.

There are many design options available to control or modify the release rate from dosage form but most common forms of oral CR delivery system fall into the reservoir, matrix, or osmotic systems. In matrix systems, the drug is embedded in the polymer matrix and drug release occurs by the partitioning of the drug into the polymer matrix and dissolution medium. Conversely, reservoir systems have a release rate controlling coat surrounding the drug molecule to control the drug release from dosage form. However, factors such as pH, the presence of food, and other physiological factors can affect drug release in normal CR systems (matrix and reservoir). Osmotic systems use the principles of osmotic pressure for drug delivery. Drug release in these systems is independent of pH and other body parameters on a large scale and it is possible to quantify the release characteristics by improving drug properties and system.[3]

Alza Corporation of the USA (now affiliated with Johnson & Johnson, USA) was the first to build an oral osmotic pump and even today, they are leaders in the industry with technology called OROS^{TM}. Oral osmotic pumps have certainly come a long way and the products available based on this technology[4] and the number of patents granted over the past few years makes their presence felt in the market. They are also known as GITS (Gastro Intestinal Therapeutic System). An important milestone in the oral NDDS is the development of the Osmotic drug delivery system, a new and highly versatile system.[5] Osmotic drug delivery system (ODDS) are different from matrix based system; delivery of active agents is driven by an osmotic gradient rather than a drug concentration in the device.[6] Osmotic devices are the

most promising systems based on drug delivery. They are among the most reliable novel drug delivery systems and can be used as oral delivery systems or injectables.[5] There are more than 240 patented osmotic drug delivery systems.[7,8]

2.0 WHAT IS OSMOSIS?

Osmosis refers to the process of movement of solvent molecules from low concentration to high concentration across the semipermeable wall. It is driven by a difference in the concentration ofthe solute across the membrane that allows the passage of water, but rejects any molecules or ions. Osmotic pressure is a pressure that, when applied to a highly concentrated solution, prevents the transport of water across the semipermeable wall.

2.1 PRINCIPLE OF OSMOSIS

The first report of an osmotic effect came to Abbe Nollet (1748), but Pfeffer obtained the first quantitative estimates in 1877.[7] In Pfeffer's experiment, membrane having water permeability but impermeable to sugar solute is used to separate a sugar solution from pure water. The flow of water then occurs in a sugar solution that cannot be stopped until pressure is applied to the sugar solution. Pfeffer has shown that this pressure, the osmotic pressure of the sugar solution, is directlyproportional to the concentration of the solution and the absolute temperature.

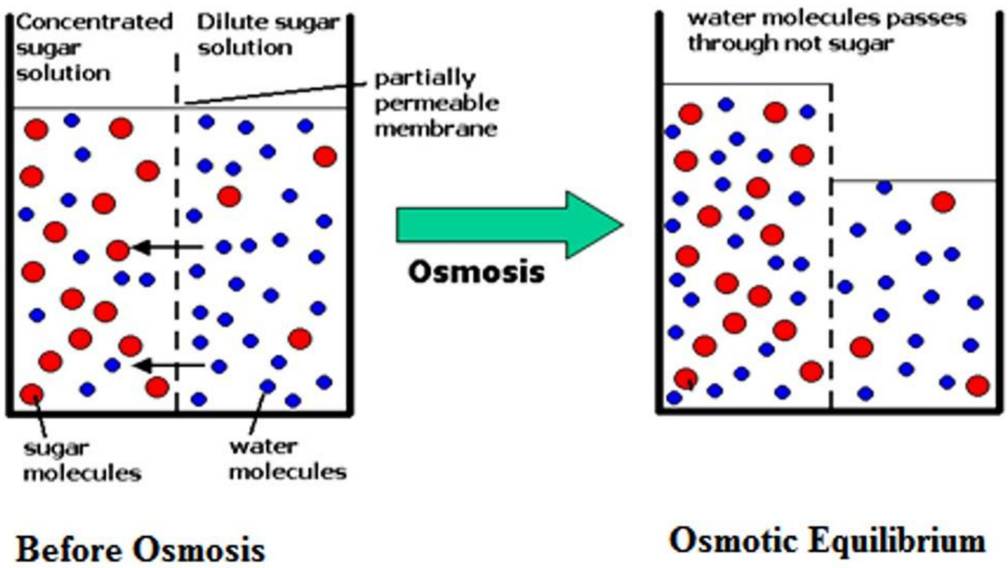


Figure 2: A schematic illustration osmotic flow and the attainment of osmotic equilibrium In a few years after, Van't Hoff has shown similarities between these results and the relevant gaslaws with this statement.

$$\pi = \phi cRT \quad \text{[1]}$$

Where ϕ is the osmotic coefficient of the solution (equal to 1 for dilute solutions) and where c is the molar concentration of sugar (or other solute) in the solution, R is the gas constant, and T the absolute temperature.

The Van't Hoff calculation presents excellent ways to calculate the osmotic pressures of the solute across SPM (semipermeable membrane) and it is also accurate with a low solute concentration. But if the membrane cannot be completely semipermeable and if allows the passage of solute and solvent, the osmotic pressure calculated by the above equation will be higher, compared to the test value. Highly concentration solutions also show differences in these relevant statistics.

Another way to find the right balance of osmotic pressure is to use vapor pressure measurements and to use the expression.

$$\pi = \frac{RT}{V}\ln\left(\frac{P_0}{P}\right) \quad \text{.....} \quad [2]$$

Where, P0 is the vapour pressure of pure solvent, P is the vapour pressure of the solution, V is the molar volume of the solvent.

Osmotic pressures for composite (highly concentrated) solutions of soluble compounds commonly used in the production of controlled release dosage form are very high, ranging from 30 atm of sodium phosphate up to 500 atm of lactose-fructose mixture.[9] These osmotic pressures can produce high water flow across SPM. Osmotic water flow across the SPM is provided by equation.[10]

$$\frac{dv}{dt} = \frac{A}{h}Lp(\sigma\Delta\pi - \Delta p) \quad \text{.....} \quad [3]$$

Where $\mathbf{dv/dt}$ is water influx, $\boldsymbol{A}$ and $\boldsymbol{h}$ are the membrane area and membrane thickness, respectively; $\boldsymbol{Lp}$ is mechanical permeability; $\boldsymbol{\sigma}$ is the reflection coefficient; and $\Delta\boldsymbol{\pi}$ and $\Delta\boldsymbol{p}$ are the osmotic and hydrostatic pressure differences, respectively, between the inside and outside of the system.

This equation is strictly true only with completely selected membranes: the membrane that allowto enters the water but impermeable to the osmogent.

Permeability of water can vary over a wide range, but most osmotic devices usually comprises water permeable ingredient. Cellulosic polymers, especially cellulose acetate, are

widely used. Typical osmotic infiltration rates for cellulosic membranes range from 1 x 10^{-5} to 1 × 10^{-7} cm^3.cm/cm^2.h.atm.

Although, there are various factors that control the specific pattern of drug delivery such as the structure of SPM, the size of the delivery orifice, the surface area and thickness of SPM, the pH, and the electrolyte concentration in the external fluid, environment and osmogen concentration etc.

3.0 CLASSIFICATION OF OSMOTIC DRUG DELIVERY SYSTEM Schematic diagram 1 shows the classification of osmotic drug delivery system. They fall in two categories.

A. Implantable Osmotic Pump
B. Oral osmotic Pump

A. Implantable Osmotic Pump

1) The Rose-Nelson Pump

In 1955, Rose and Nelson applied the principle of osmotic applied to drug delivery for the first time.[11] They described two systems that were able to deliver drug at controlled doses of 0.02 ml / day for 100 days and 0.5 ml / day for four days. A schematic diagram of the Rose-Nelson pump is given in figure 3A. The device has three chambers, first one is a drug chamber, second one is a salt chamber and third one is a water chamber. The salt chamber is separated from the water chamber by an semipermeable solid membrane, while the drug chamber is separated from the salt chamber by an elastic diaphragm. Over time, the osmotic imbibation of water through the SPM (semipermeable membrane) increases the volume of the salt chamber, disrupting the elastic diaphragm that eventually extrude the drug from the delivery system through the delivery orifice. The osmotic pressure (of the saturated salt solution in the chamber) is the driving force for release of the drug from the system. Therefore, as long as enough solid salt remains in the salt chamber, the water penetration rate through the SPM is constantly same, producing a constant rate of drug release.

One of the problems with the Rose-Nelson pump is that the osmotic flow occurs as soon as the salt chamber meets the water. Therefore, the pump had to be kept empty and to be loaded with water immediately before use, which make a process that was problematic for delivery of drugs. Moreover, although these systems have a large amount of research, their complex design makes them poor system in large-scale production which makes them of limited use.

The Rose-Nelson pump rate is provided by Equation.

$$\frac{dM}{dt} = \frac{dV}{dt} * C \quad \text{..... [4]}$$

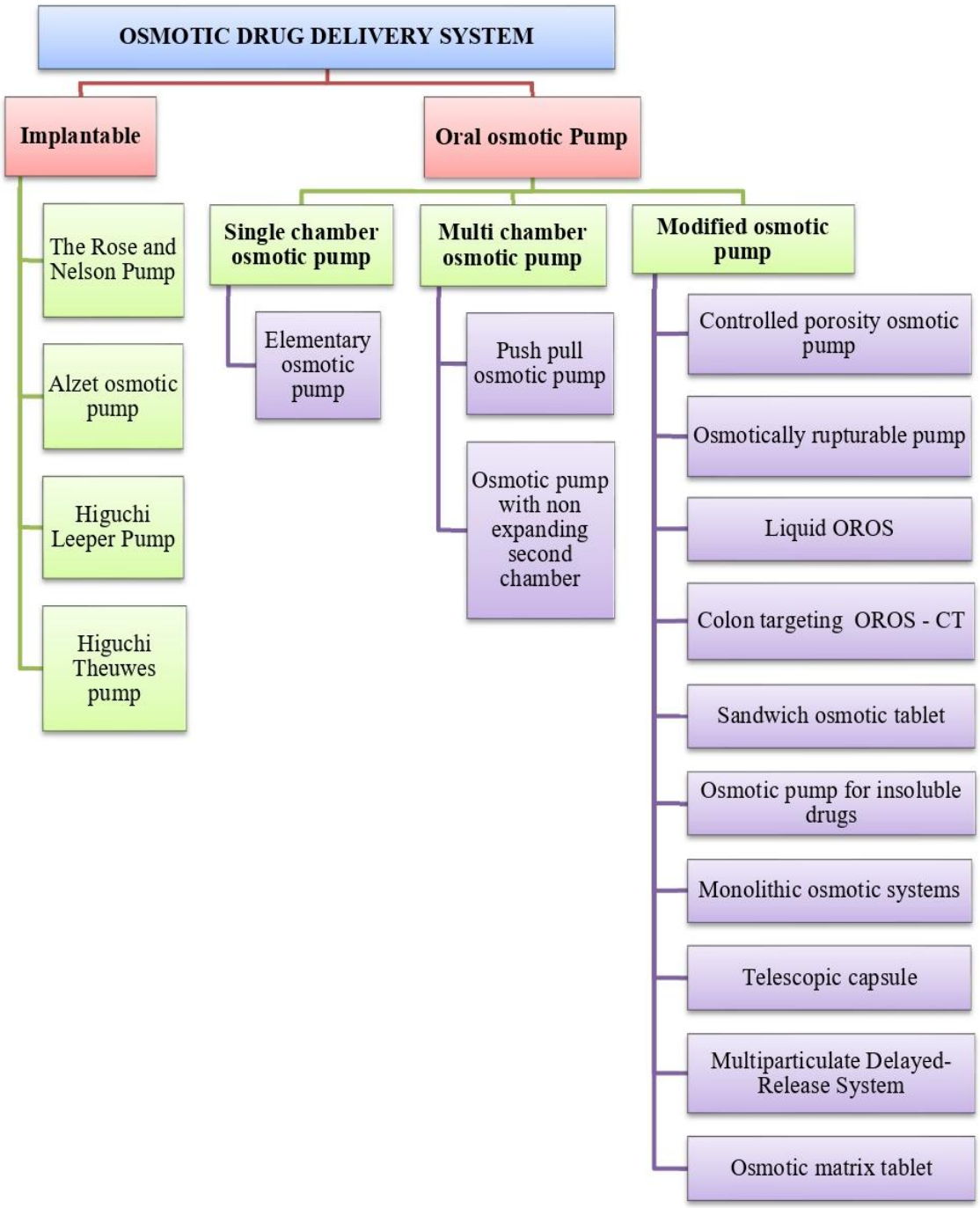
Where dM,/dt is the drug release rate, dV/dt is the volume flow of water into the salt chamber, and c is the concentration of drug in the drug chamber.

2) Alzet osmotic pump[12,13]

ALZET pumps (figure 3B) operate due to the difference in osmotic pressure between the inner chamber of the pump, called the salt sleeves, and the area of tissue where the pump implanted. Thewater flux into the tap through the SPM due to the high osmolality of the salt sleeve that forms the outer side of the pump. When water enters the salt sleeve, it compresses the flexible reservoir, removing the test solution from the pump at a controlled, pre-determined rate. Limitation of pump is that pumps are designed for single use only because compressed reservoir cannot be refilled.

3) Highuchi – Leeper Pump[14,15,16, 37]

In the 1970's, Highuchi and Leeper introduced a series of modifications to Rose Nelson's pump. A major modification of their plans is the removal of the water chamber from the device and the imbibing of water from the external environment with SPM. The formal representation of the pump is shown in Figure 3A. The importance of the invention lies in the fact that the system does not work until it is placed in a liquid environment and can be stored for weeks or months before use. However, the complex structure and number of pump components still makes it unpopular in largescale production.



Schematic Diagram 1: The classification of osmotic drug delivery system.

4) Highuchi – Theeuwes Pump[15,17, 37]

In the early 1970's, Higuchi and Theeuwes developed another, similar to the simplification of the Rose-Nelson pump. As shown in Figure 3A, the pump contains a SPM that surrounds a layer of solid salt. The interior of the salt layer is coated with a flexible diaphragm, which touches the interior of the device containing an active drug compound. Like a Higuchi-Leeper tap, the water to perform the osmotic action of the pump is require to

obtained in the surrounding aqueous environment. On the Higuchi-Theeuwes system, however, the rigid housing is dispensed with the membrane acts as the outer casing of the pump. This membrane is very strong and strong enough to withstand the pressure of the pump made inside the system. The device is loaded with the desired drug before use. When the machine is placed in a liquid environment, the drug release follows the time course set by the salt used in the salt chamber and outer membrane casing permeability. Most Higuchi-Theeuwes pumps use a solid salt disperser in a suitable salt chamber of the system.

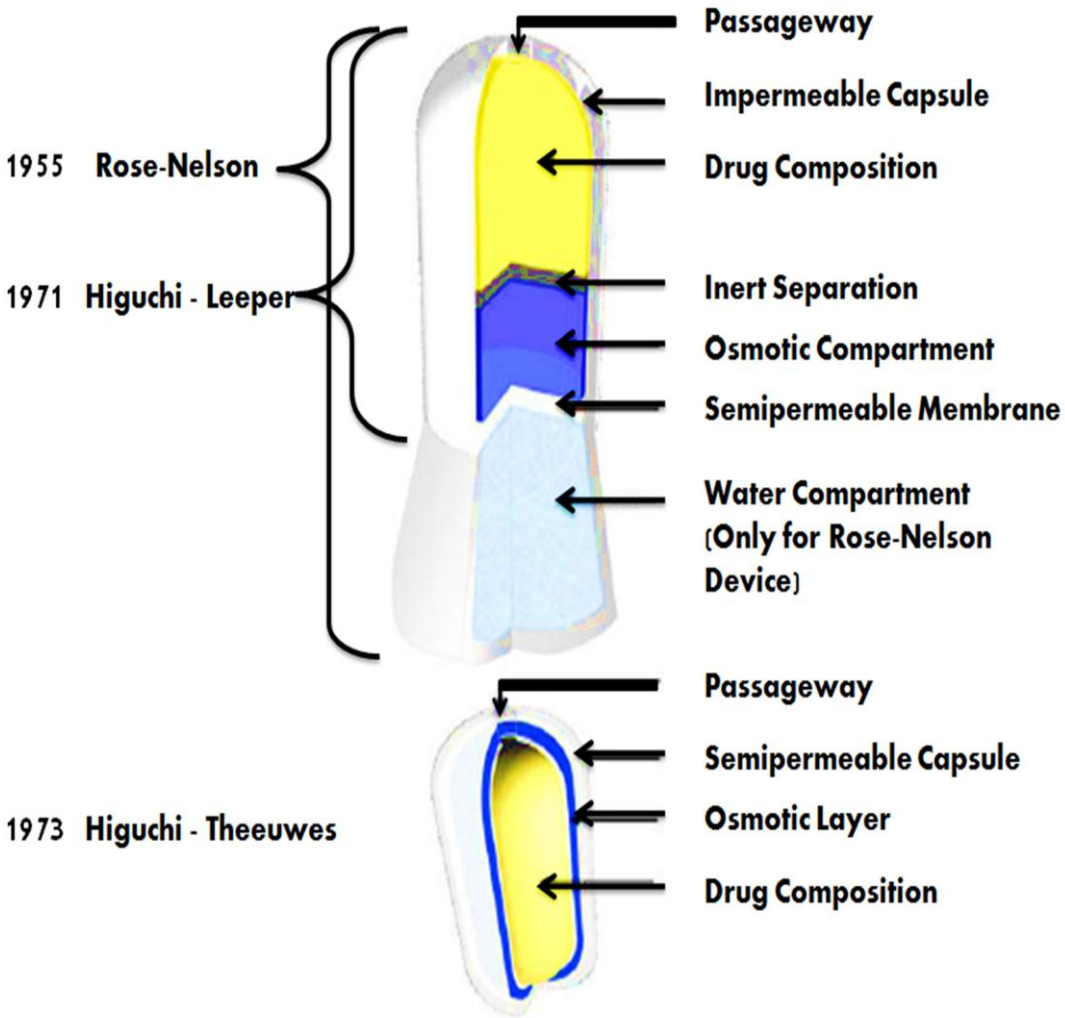


Figure 3A: Schematic diagram of Osmotic Pump of Rose-Nelson, Higuchi Leeper and Higuchi – Theeuwes.[37]

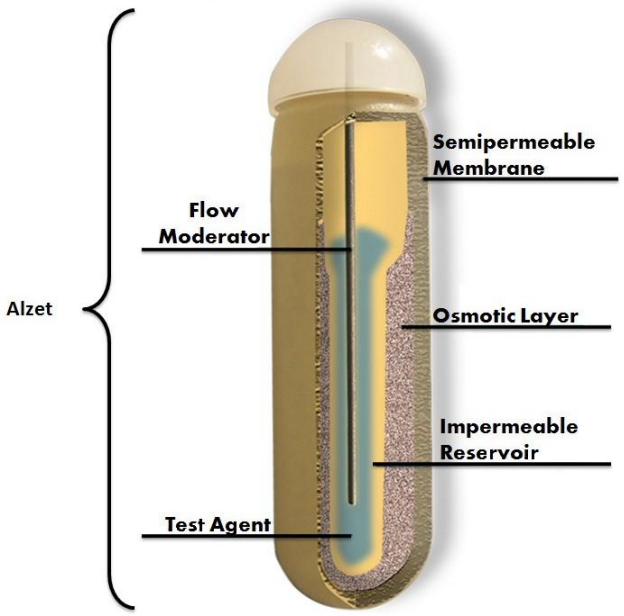


Figure 3B: Schematic diagram of Alzet Osmotic Pump.

B. Oral Osmotic Pump

1) Single Chamber Osmotic Pump

i. Elementary Osmotic Pump

The great development of the osmotic pump came in 1975, when Theeuwes continued to simplify the Rose-Nelson pump and developed a system known as the elementary osmotic pump.[10] The basic osmotic pump consists of an osmotic core surrounded by an SPM consisting of the orificefor drug delivery. The formal representation of the pump is given in Figure 4.

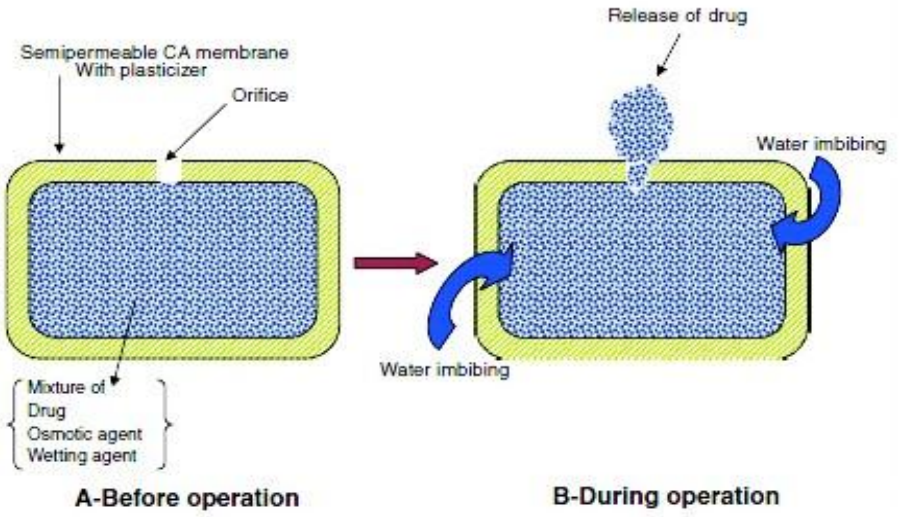


Figure 4: Elementary Osmotic Pump (EOP).

When placed in a liquid environment, the difference in osmotic pressure draws water to the tablet through a SPM, and forms a complete solution inside the EOP. Continuous water intake increases the volume of the tablet and leads to the formation of hydrostatic pressure within the tablet. As the system is surrounded by an SPM, hydrostatic pressure is released from the solution of a complete drug solution through the delivery orifice. The process continues at a steady rate until all the soluble core is completely dissolved. Once it dissolve completely, drug delivery continues at declining rates until the osmotic pressure difference across the membrane approaches zero.

Drug discharge (dv / dt) from low osmotic tablets is defined by equation 3. When designing a basic osmotic pump, the following factors may affect the delivery rate and should be considered. These materials, which also apply to other types of osmotic pumps are solubility of core component, osmotic pressure, membrane structure and orifice size for drug delivery.

Equation 3 indicate that the rate of drug release from the primary osmotic pump depends on the solubility of an osmotic core components. Therefore, another way to control the rate of drug release is to reverse the solubility of the osmotic core components. This is possible by changing the selection and the number of osmotic agents.

The next important factor in controlling osmotic drug delivery is the difference in osmotic pressure across the membrane. For zero-order drug release, the osmotic pressure difference should immediately reach a constant value and remain constant during the desired release period. In osmotic pumps, this is achieved by keeping a saturated solution of the drug in the core. If a drug solution not suffice to create sufficient osmotic pressure, additional osmotic agents should be added to the core formulation. Table 2 provides a list of common osmotic agents and the corresponding osmotic pressure of their saturated solutions. As seen in Table 2, the osmotic pressures vary widely and as a result wide range of drug release rate can be achieved by selecting the appropriate osmotic agents.

As can be seen in equation 3, the membrane properties is another factor that controls drug release. The membrane should be selectively permeable to the water only, allowing water to enter the tabletat a controlled rate. Examples of polymers used as coating in osmotic delivery systems include cellulose esters such as cellulose acetate, cellulose diacetate, cellulose triacetate, cellulose propionate, cellulose acetate butyrate and others.[17] Other polymers used are ethylcellulose[18] and Eudragits.[19]

The size of the drug delivery orifice is also important in controlling the rate of release. For elementary osmotic pumps, the size of the delivery orifice should satisfy two conditions. Firstly, it should be sufficient enough to reduce the hydrostatic pressure within the tablet which may affect the zero-order discharge rate and secondly, it should be small enough to reduce its contribution to complete drug release with easy drug diffusion through delivery orifice. There are equation available for estimating the minimum and maximum width of the orifice area.[10]

Table 2: Osmotic Pressure of Saturated Solutions of Common Pharmaceutical Solutes

Compound or Mixture	Osmotic Pressure (atm.)
Lactose-fructose	500
Dextrose-fructose	450
Sucrose-fructose	430
Mannitol-fructose	415
Sodium chloride	356
Fructose	335
Lactose-sucrose	250
Potassium chloride	245
Lactose-dextrose	225
Mannitol-dextrose	225
Dextrose-sucrose	190
Mannitol-sucrose	170
Sucrose	150
Mannitol-lactose	130
Dextrose	82
Potassium sulfate	39
Mannitol	38
Sodium phosphate tribasic. 12 H2O	36
Sodium phosphate dibasic .7 H2O	31
Sodium phosphate dibasic. 12 H2O	31
Sodium phosphate dibasic anhydrous	29

2) Multi Chamber Osmotic Pump

i. Push Pull Osmotic Pump

This device is a modified elementary osmotic pump and is an osmotically multi-chamber tablet. These osmotic pumps have two chambers and are divided into two main sections depending on whether one chamber expand into the other or the chambers are rigid and do not expand.

Tablets containing expansion (push) layer are the most important one.[22,23] This device is designed for the delivery of drug with poor water solubility and is indicated by a scheme in figure 5.[37] It consists of two layer, surrounded by an impermeable solid membrane. The

upper (pull) layer contains drug and is connected to the external environment by the delivery orifice. The lower (push) layer has a polymeric agent and has no delivery area. When the dosage form comes in contact with a liquid environment, water is osmotically driven into both parts. Because the lower chamber does not have any delivery area, it expands and pushes the pull layer into the upper side (toward delivery orifice), transmitting the drug in the solution form through a delivery orifice.

The drug solution diluted by the following two steps.

a) Osmotic water imbibition solubilize drug in the pull chamber. However, the drug cannot escape the device unless it passes through a second chamber.

b) Because the water osmotically drawn into the second chamber, the passage to the second chamber dilute the drug solution before leaving the delivery system.

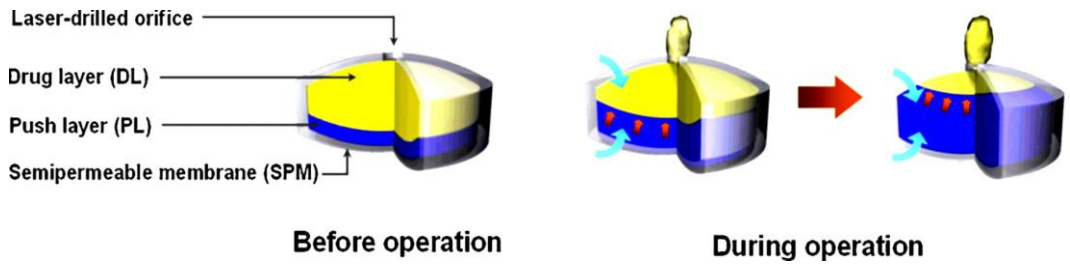


Figure 5: Mechanism of Drug Delivery from a Push-Pull.

ii. Osmotic Pump with Non-Expanding Second Chamber

These multichamber devices contain systems that contain a non-expandable second chamber. The purpose of the second chamber is to dilute the drug solution leaving the device (which is very useful in treating drugs with a severe GI irritation) or simultaneous delivery of two drugs. Poorly or insoluble drugs can also be delivered by formulating them into this type of device.[2]

3) Modified Osmotic Pump

i. Controlled Porosity Osmotic Pump (CPOP)

The controlled osmotic porosity pump contains water-soluble additives in the coating membrane, which after contact with liquid environment, it dissolves and results in the formation of a microporous membrane in situ, as shown in (Figure 6).

The controlled porosity wall can be described as having a sponge-like shape. Generally, materials that produce from 5 to 95% pores with a pore size from 10A - 100µm can be

used.[21,22,24,25] The resulting membrane is permeable to both, dissolved solute and water. Water-soluble additives used for this purpose are dimethyl sulfone, saccharides, amino acids, sorbitol, etc.[26] Ying-Ku Lin (2003) studied the mechanism of release of moderate-to-high-soluble drugs using various solubility modifying agents.[27]

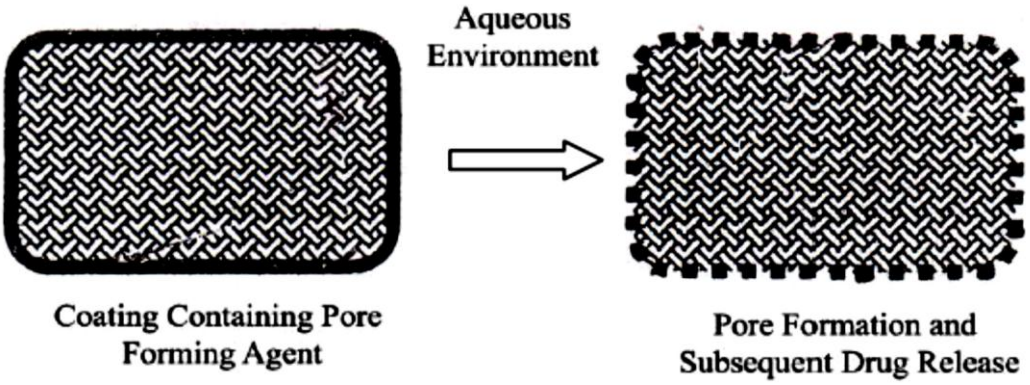


Figure 6: Controlled Porosity Osmotic Pump (CPOP)

ii. Osmotically Rupturable Pumps

Another popular category is the osmotic systems that release the active ingredient through an osmotic bursting device. The system was developed by Baker and consists of an osmotic core surrounded by an SPM.[28] When it placed in a liquid environment, water is osmotically drawn into this device, which leads to swelling of the membrane. This process continues until the internal pressure inside the device becomes greater than the cohesive force of the membrane and the membrane breaks down in a weak area, usually around the edges. When the membrane is raptured,the device becomes like a elementary osmotic pump and the drug compound is pulled out from thecracked area with mechanism of osmotic pumping.

Rapture time of SPM can be controlled by.

a) Varying type, area or thickness of SPM
b) Altering the osmotic agents embedded in the osmotic core.

iii. Liquid Oral Osmotic System (L-OROS)

The various LOROS systems available to provide controlled delivery of liquid formulations include a L-OROS soft cap, L-OROS hard cap and a delayed liquid bolus delivery system. Each of these systems includes a layer of liquid drugs, an osmotic engine or a Push layer and a SPM (Figure 7).

When this system comes in contact with a water, the water penetrate inside the layer through

SPM and will activate an osmotic layer. The expansion of the osmotic layer leads to the formation of hydrostatic pressure within the system, thereby forcing the liquid formulation to extrude it from orifice at the delivery site.[1] While, L-OROS hard caps and L-OROS soft cap systems are designed to provide continuous drug delivery, the L-OROS delayed delivery of liquid bolus system is designed to deliver pulse of liquid drug.[29]

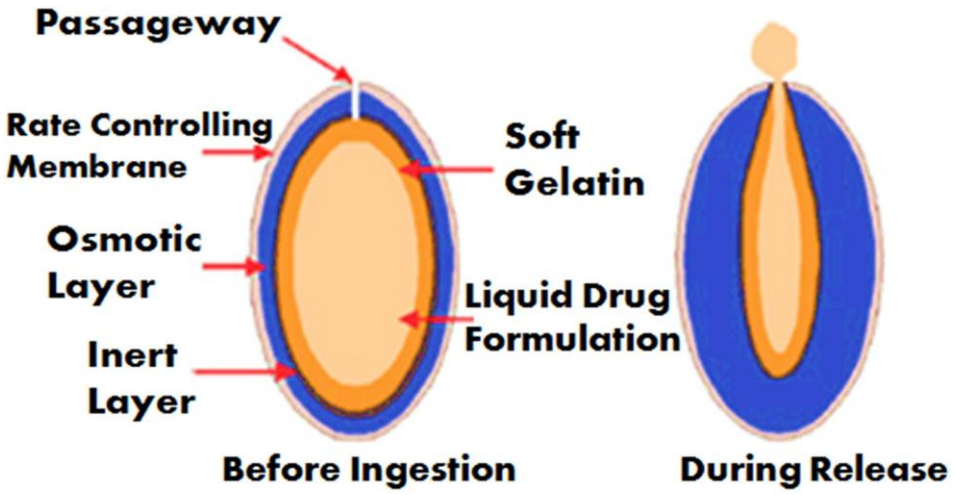


Figure 7: Cross-sectional Diagram of Liquid Oral Osmotic System (L-OROS).

iv. Colon Targeted Oral Osmotic System (OROS-CT)

OROS-CT is used to make once or twice a day the delivery of drug to the colon region. It comprises hard gelatin capsule filled with 5-6 enteric-coated push-pull osmotic units for targeted drug delivery to colon region.[30] After contact with GI fluid, the gelatin capsule dissolves but the enteric coating will prevents the entry of fluid from the stomach fluid into the system (Figure 8).

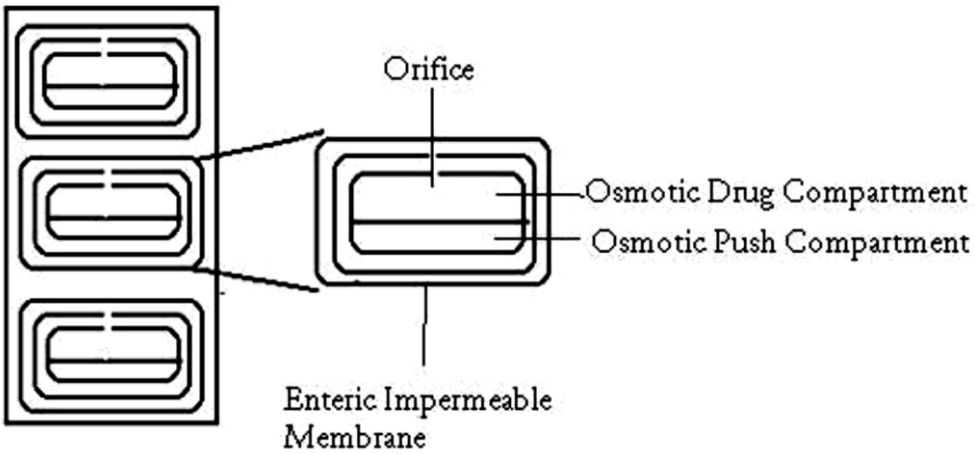


Figure 8: Cross-sectional Diagram of OROS-CT Delivery System.

As the OROS-CT system enters the small intestine, the enteric coating dissolves and water drawn into the core, that causing swelling of push layer. At that time, a flowable gel is formed into the drug layer, which is then released out of the orifice at a rate that is precisely controlled by the water transport rate of water across the SPM. About 80% of the drug is delivered to the large intestineby OROS-CT.

v. Sandwiched Osmotic Tablets (SOTS)

It consists of a polymeric push layer sandwich between two layers of the drug with two delivery orifices.[1] When placed in a liquid environment (Figure 9)[31] the central push layer containing the swellable polymer start to swell and the drug start to release from the delivery orifice. The advantage of this type of system is that the drug is extruded from two opposite side layers of the tablet and therefore SOTS may be suitable for drugs that tend to cause local irritation of the abdominal cord (gastric mucosa).

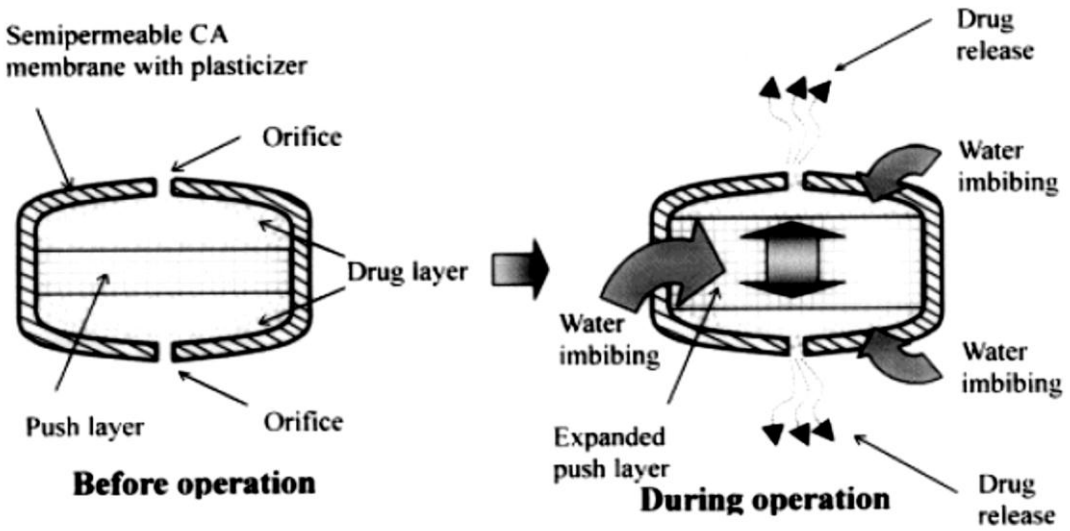


Figure 9: Schematic Diagram of Sandwiched Osmotic Tablet (SOTS).

vi. Osmotic Pump for Insoluble Drugs

It consists of coating the particles of the osmotic agent (osmogens) with a SPM. These particles are mixed with an insoluble drug substance and pressed in the form of a tablet, after which theyare encased in a SPM, and an orifice is formed on the membrane.

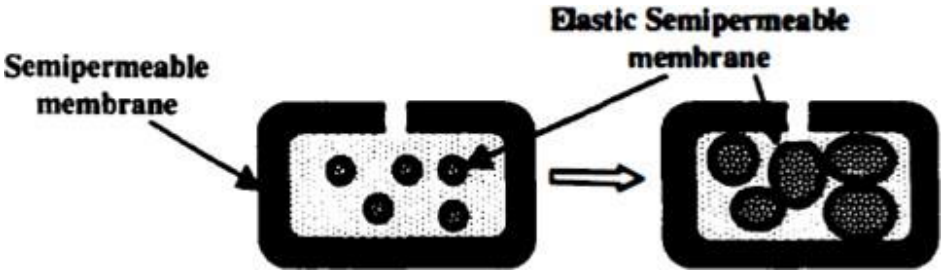


Figure 10: Modified osmotic pump for insoluble drugs[32]

After its contact with the liquid, the water is drawn through both layers to the particles of the osmotic agent, then swells and push the drug hydrostatically through a delivery orifice.[32]

vii. Monolithic Osmotic Systems

It comprises a simple dispersion of a water-soluble substance in a polymeric matrix. When the system comes in contact with a liquid environment, the water uptake by the drug substance occur that rupture the polymer matrix, thereby releasing drug to the external environment. Initially, this process takes place in the outer surface of the polymer matrix, but gradually progresses to the inner surface of the matrix in a consistent manner. However, this system fails if more than 20 to 30% of the active agent incorporated into the osmotic system.[33]

viii. Telescopic Capsule for Delayed Release

The device has two chambers, the first contains the delivery orifice and drug, and the second contains the osmotic engine.[34] A wax like layer separates the two chamber. To assemble the delivery device, the drug substance is placed in one of the chamber with a manual or automatic filling mechanism. A two layer tablet with an osmotic engine is placed on the part of the capsule cap with a convex osmotic layer shown at the end of the cap and a barrier at the end of the closed cap and a barrier layer is exposed at the opening of cap. The filled vessel open end is fitted to innerside of the cap's open end followed by compressing the two pieces together till the osmotic bilayer tablet, cap, and vessel fit tightly together. When fluid enter in the housing of the dispensing device, it will expand the osmotic engine resulting in exerting pressure on the slid able connected sections of second and first wall. Which leads to the flow of surrounding fluid driven by the pressure that enter the reservoir, is minimal, and consequently no agent will deliver during that the period.

ix. Multiparticulate Delayed-Release System

In this system, pellets comprising water soluble drug optionally with osmotic agents are

coated with a SPM. When it comes in contact with water, water enters the core and forms a saturated solution of drug substances. The osmotic pressure gradient causes fluid influx, leading to rapid fluid enlargement that cause expansion of membrane and the formation of pores. The release of drug ingredients through these holes usually follows zero-order kinetics. In studies conducted by Schultz and Kleinebudde[35], it was found that lag times and release rates depend on the level of thickness of coating layer and the osmotic pressure of the dissolution media.

x. Osmotic Matrix Tablet (OSMAT)

It is an osmotically operated matrix system, which uses hydrophilic polymer material to swell and gel into a liquid that makes it semi-permeable in situ. Release from such a matrix system containing osmogent, therefore, it can be modulated by phenomena of the osmosion. OSMAT thus follow both matrix and osmotic aspects leading to quantum improvement in drug delivery from swellable matrix systems. Osmotic matrix tablets are very easy to produce and does not require SPM coating and orifice for drug delivery. Therefore, it is a less expensive technology and can be utilized for a variety of drugs.[36, 38]

4. MAJOR COMPONENTS OF OSMOTIC DRUG DELIVERY SYSTEM

The following are the elements used in building an osmotically controlled system.

(1) Osmogents

Osmogents are an most important ingredient in osmotic device. When biological fluid enters the osmotic pump through a semipermeable membrane, osmogent dissolve in the biological fluid, creating osmotic pressure inside the pump and pushing the drug out of the pump through an orifice. Various osmogents Includes inorganic salts and carbohydrates. Mostly, potassium chloride, sodium chloride, and mannitol are used as osmogens. Table 2 enlist different osmogents along with it's osmotic pressure.[38, 39, 40]

(2) The Semipermeable membrane

Any polymer allowed to enter the water but not resistant to mixing can be selected as component for semipermeable membrane. Cellulose acetate is a commonly used polymer for the preparation of osmotic pumps. It is found in various acetyl content labels. In particular, acetyl content of 32% and 38% is widely used. Acetyl content is defined by the degree of substitution (DS), i.e., the average number of hydroxyl groups in the anhydroglucose polymer unit replaced by the substituting group. Other polymers that can be used for the above purpose include cellulose esters such as cellulose acetate, cellulose

diacetate, cellulose triacetate, cellulose propionate, cellulose acetate butyrate, and cellulose ethers such as ethyl cellulose. In addition to cellulose derivative, other polymers such as agar acetate, amylose triacetate, betaglucan acetate, poly (vinyl methyl) ether copolymers, poly (orthoesters), poly acetals and selective poly (glycolic acid), derivatives of poly (lactic acid), and Eudragits can be used as non-linear film formulations.[38, 40]

(3) Coating Solvent

Solvents suitable to prepare a polymeric solution to be used to produce the semipermeable membrane of an osmotic device include inorganic and inorganic solvents that do not damage the environment and other materials. Typical solvents include isopropyl alcohol, methylene chloride, acetone, butyl alcohol, ethanol, ethyl acetate, cyclohexane, carbon tetrachloride and water. Different solvent can be used in various proportion such as acetone-water in ration of 90:10, Ethanol: acetone in ration of 20:80 and like.[38, 40]

(4) Plasticizers

Plasticizers were added to alter physical structures and improve the film-forming properties of polymers. Plasticizers can significantly alter the viscoelastic properties of polymers. Plasticizers increase the efficiency, flexibility, and permissibility of covering solvents. Polyethylene glycol, dibutyl sebacate, triacetin, ethylene glycol diacetate, ethylene glycol monoacetate, diethyl tartrate and triethyl phosphate can be used as a plasticizer in construction semipermeable membrane.[38, 40]

(5) Pore Forming Agents

Pore forming agents are added in the coating system to create in situ porous stracture in the coating film to increase water permeability of coating film as well as to allow to releasee drug from the dosage form. Various pore former such as sodium chloride, calcium chloride, mannitol, poloxamer, PVP, water soluble lower molecular weight polymer, sorbitol, mannitol, etc can be used as pore-forming agents.[38, 40]

(6) Polymers

These polymers are used in the formulation of osmotic systems to constitute a drug layer. Highly water-soluble drug can be trapped in hydrophobic matrix and medium-soluble drug can be added to hydrophilic matrices to obtain more controlled release. Typically, a mixture of hydrophilic and hydrophobic polymers has been used in the formation of osmotic pumps of water-soluble drugs. The selection is based on the drug solubility, it's the amount of drug

and rate of drug release from the dosage form. Polyethylene Oxide and Hydroxy ethyl cellulose are most widely used polymer for osmotic dosage form. Other hydrophilic polymers such as carboxy methylcellulose, hydroxy propyl methylcellulose, poly (vinyl pyrrolidone), and hydrophobic polymers such as ethyl cellulose can be used for this purpose.[38, 40]

(7) Solubilizing Agents

In the osmotic delivery system, the most soluble drugs in the water can show a maximum release rate of about zero order. Therefore, many drugs with low internal solubility are poor in osmotic delivery. However, it is possible to increase the solubility of the drug within the dosage form by addition of solubility enhancing agent. The addition of solubilizing agents to the main tablet significantly increases drug solubility.[38, 40]

(8) Wicking Agents

The wicking agent is defined as a material being capable to draw the water inside the a dynamic network of delivery device. Wicking agents are those agents that help to increase the area of contact with the drug with strong incoming fluids. The use of a wicking agent helps to increase the level of the drug release from the orifice of the dosage form. The function of the wicking agent is to manage the water in the inner surface of the tablet, thus creating channels or a network of expanded surface area. Examples are colloidal silicon dioxide and Sodium lauryl sulfate.[38, 40]

5. FACTOR AFFECTING THE RELEASE RATE OF DRUG FROM OSMOTIC SYSTEM

The drug release from osmotic delivery device depends on many process and formulation variables, including curing treatment, plasticization, and properties of the core. Besides the water solubility of the drug, the solubility of the other core ingredients can also have a major influence on the drug release by generating an osmotic pressure gradient across the polymeric coating upon interaction with dissolution medium. The rate of drug release from osmotic pumps is dependent on the total solubility and the osmotic pressure of the core (drug). Various factor that affect the release of drug from osmotic system are follows.

1. Thickness of Semipermeable Membrane

The factor that controls the rate of water infiltration is the circulation of the membrane. Proper andefficient selection of SPM sizes is one of the best ways to get regular dose release of drugs from the osmotic systems. As the tension increases, the resistance of the membrane

to the water supply increases and the water level in the embibing decreases and, in turn, the absorption rate of the tablet's spine decreases, leading to a decrease in drug release. Usually the rate of drug release can be achieved by varying the membrane, while small changes up to 5 percent can be best achieved by varying the membrane size.

2. Delivery orifice size

The orifice is one of the most important components in the lining of the drug. The size of the orifice should be adjusted to control the release of the drug into the osmotic system. It was reported that there was an appropriate orifice size range for the osmotic system; this should be less than the maximum limit for the contribution to the level of delivery made by orifice distribution. Also, they should be larger than the minimum limit, reducing the hydrostatic pressure within the system.

3. Drug Solubility

In the case of EOP, solubility of drug is one of the most important factors affecting the release of drug kinetics from osmotic pumps. Thus the lower intrinsic solubility of drug can preclude them from assembling an osmotic pump with EOP design. The drug of choice for osmotic delivery should be soluble within a range of 50- 300 mg / ml.

4. Plasticizer Amount

Plasticizers were added to transform the visible structures and improve the film-forming feature of the polymers. Plasticizers can convert polymer solid and thin to a softer, more flexible material and make it more resistant to mechanical pressure. The polymer can affect the penetration of the polymer films can lead to a level of drug release from osmotic tablets.

5. Osmogent Amount

One of the key emissions controls to be developed is the osmotic pressure gradient inside the roomand the outside environment. Since the osmotic pressure in GIT remains relatively low, the osmagent that provides the highest osmotic pressure will work with the power to drive water imbibition with tablet coverage. Therefore, the amount of osmotic agent also has a significant impact on drug release and the rate of drug release has increased with the osmogent value due to the increase in fluid, which is why it increases the drug release capacity. This can be reversed by the appropriate selection of the delivery agent (the pore agent) to achieve the desired release profile.

6. ADVANTAGES AND APPLICATIONS OF OSMOTIC PUMPS

In general, oral dosing programs that are able to release the drug at a continuous rate of given time are of great interest. These systems are able to maintain a consistent and consistent dose of thedrug in the blood and other tissues over time, with the following benefits.

a. Small amounts of an effective compound are often required to achieve the same therapeuticaction.
b. A reduced dose of a controlled drug reduces the increase in side effects, greatly improving thedrug safety profile.
c. Patient consistency is often improved with these types of scale forms, as the frequency oftreatment decreases.

In addition to these general benefits shared by other controlled release volume forms, osmoticpumps have several other distinct benefits, such as the following[3,10]

a) Osmotic pumps can be built to deliver a large portion of their content at zero-order level. This feature will allow for higher availability, as well as better control of plasma concentration.
b) Osmotic pumps can be arranged to deliver the drug at pre-set prices. This feature benefits fromsystematic treatment with most medications available.
c) The release of drugs from the osmotic pumps can be highly dependent on changes in pH, pressure and hydrodynamic conditions that occur in the intestinal tract. This feature allows osmotic pumps to display important in vitro / in vivo interactions.
d) The level of in vitro delivery can be accurately predicted using mathematical calculations, which, in turn, carry high integration with the in vivo delivery rate.
e) Delivery rate is much higher than can be obtained by size-based processes of comparable size.This is especially important when large doses of drugs have to be made.
f) Separate of the intensive drug delivery from the stomach contents and GI mucosa is beneficial in the case of hydrolysis-prone drugs in the GIT and those that may cause irritation to the mucosa.

7. CURRENTLY MARKETED AND UNDER DEVELOPMENT DRUG FORMULATION BASED ON OSMOTIC DRUG DELIVERY SYSTEM

Overall, the benefits associated with osmotic pumps have made them an attractive form factor for the delivery of a wide range of functional items. Table 3 provides a list of the most common osmotic systems available for the delivery of various drugs. The variety of

therapeutic drugs included in Table 3 is a testament to the flexibility and flexibility of osmotic pumps as drug delivery systems.[37, 41]

Oral osmotic pumps have also been used successfully in veterinary medicine. One example is a specially designed oral osmotic pump that is able to deliver Ivermectin to cattle at various levels controlled by zero-order for 35 days.

Table 3: Marketed oral osmotically driven products classified according to therapeutic indication.

Product / Brand Name	Active	Form	Strength (mg)	t1/2(h)	Developer/marketer
Cardiovascular disorders					
UT-15C	Treprostinil diethanolamine	SEOP	1	4	UnitedTherapeutics
LCP-Lerc	Lercanidipine	DOEOP	20	3	Osmotica /Recordati
Cardura CR	Doxazosin mesylate	PPOP	4–8	15–22	Alza / Pfizer
Concerta	Methylphenidate HCl	PSOP	18–54	2–4	Alza / McNeil
Ditropan XL Ditropan UD /Tavor	Oxybutynin chloride	PPOP SEOP	5–15	12–16	Alza / UCB Pharma Osmotica/ Phoenix
Teczem	Enalapril Diltiazem	CPOP	280 5	11	Merck / Aventis
Tiamate Dilacor XR	Diltiazem HCl	CPOP SCOT	120–240	3–4.5	Merck/Aventis Andrx
Covera HS	Verapamil HCl	COER	180–240	2–5	Alza/Pfizer
DynaCirc CR	Isradipine	PPOP	5–10	8	Alza/Novartis
Minipress XL or Alpress LP	Prazosin	PPOP	2.5–5	2–4	Alza/Pfizer
Procardia XL / Adalat CCNifed Sol	Nifedipine	PPOP DOEOP	30–90	2–5	Alza / Pfizer –Bayer Osmotica /Phoenix
Metabolic disorders					
Topamax	Topiramate	PSOP	25–175	21	Alza
AltoPlus XR	Metformin HCl Pioglitazone HCl	SCOT	500–850 15	5.2	Andrx / Takeda
Fortamet	Metformin HCl	SCOT	500–1000	5.2	Andrx
Altoprev	Lovastatin	EOP	10–60	1.1–1.7	Andrx
Glucotrol XL	Glipizide	PPOP	2.5–10	2–4	Alza / Pfizer
Nervous and neuronal disorders					
Flexeril XL	Cyclobenzaprine	EOP	15–30	18	Alza
Oxycontin	Oxycodone	PPOP	10	~3	Alza
Jusnista	Hydromorphone	PPOP	8–64	2–3	Alza / J&J
Invega	Paliperidone	PPOP	3–12	23	Xian – Janssen
Elafax XR	Venlafaxine HCl	EOP	37.5–150	3–7	Osmotica /Phoenix
Tegretol XL	Carbamazepine	SEOP	100–400	25	Alza / Novartis
Osmosin	Indomethacin	EOP	75	2.6–11.2	Alza / Merck
Teosona Sol	Theophylline	DOEOP	400	5–8	Osmotica / Phoenix
Respiratory and Seasonal disorders					
Allegra D 24 h	Pseudoephedrine HCl	DOEOP	240	9–15	Osmotica / Aventis

	Fexofenadine HCl		180	14.4	
Loremex	Pseudoephedrine HCl	DOEOP	240	5–8	Osmotica /Phoenix
	Loratadine		10	–	
Mildugen D	Pseudoephedrine HCl	DOEOP	240	5–8	Osmotica /Phoenix
	Astemizole		10	26	
Efidac 24 brompheniramine	Pseudoephedrine HCl	EOP	240	5–8	Alza / NovartisOTC
	Brompheniramine		16	–	
Efidac 24 chlorpheniramine	Pseudoephedrine HCl	EOP	240	5–8	Alza / NovartisOTC
	Chlorpheniramine		16	21–27	
Efidac 24 Sudafed 24 hMex:24	Pseudoephedrine HCl	EOP EOP DOEOP	240	9–16	Alza / Novartis OTC Alza / J&JOsmotica /Phoenix
Volmax	Albuterol	EOP	4–8	2.7–6	GSK / Muro Pharmaceuticals
Acu System C	Vitamine C	CPOP	n.p.	n.p.	Alza
Acutrim	Phenylpropanolamine	DOEOP	75	3–5	Alza
Gastrointestinal disorders					
Osmoran 300	Ranitidine HCl	DOEOP	300	2–4	Osmotica /Phoenix

8. CONCLUSION

Osmotic pumps are one of the most controlled drug delivery programs. Osmotic drug delivery systems usually contain a drug compound containing osmogent in the core coated with an semipermeable membrane. This coating has one or more delivery holes from which the solution or suspension of the drug is released over time period. In osmotic delivery systems, osmotic pressure depletes the ability to release drugs through delivery hole from the dosage form. Increasing the pressure inside the dosage form from the water penetration causes the drug to be release from the dosage form. Major benefits include precise control of zero-order over the extended period of time — precise release rate can be obtained regardless of the environmental factors at the delivery site. Precise controlled rate of drug release by osmotic systems also lowers the profile of the side effect by moderating blood plasma concentrations of normal-dose forms (e.g., conventional immediate release). Therefore, most of the products on the market right noware based on drugs used to treat long-term diabetes, high blood pressure, attention deficit disorder, and other chronic illnesses. In addition to the osmotic delivery systems, implants acting on osmotic systems are auspicious for the delivery of varying molecules at a precise rate over extended period of time. In the future, various efforts are being made to produce a successful osmotic system such as pulsatile delivery in terms of expandable orifice, lipid osmotic pump, telescopic capsule containing a small osmotic pump for delayed discharge, an osmotic bursting osmotic pump, and so on.

REFERENCES

1. Verma, R.K., Mishra, B. and Garg, S., Osmotically controlled oral drug delivery, Drug Dev. lnd. Pharm, 2000; 26: 695-708.
2. Verma, R.K., Krishna, D.M. and Garg, S., Formulation aspects in the development of osmotically controlled oral drug delivery systems, J. Contr. Release, 2002; 79: 7-27.
3. A. Anka Rao, V. Narasimha Rao, A. Seetha Devi, et al. Oral controlled release drug delivery system: an overview. International Journal of Pharma and Chemical Research, 2015; 1(1): 6-15.
4. R.K. Verma, S. Garg, Current status of drug delivery technologies and future directions, Pharm. Technol.-On Line (http: / /www.pharmaportal.com), 2001; 25: 1–14.
5. Jerzeweski, R.C., Chien, Y.W., Osmotic drug delivery In: Kydonieus, A. (Ed). Treaties on controlled drug delivery: Fundamental, optimization, application, Marcel Dekker, Inc. New York, 1992; 225-253.
6. Ende, M.T., Herbig, S.M., Korsmeyer, R.W. and Childlaw, M.B., In; Wise, D.L., (Ed)., Handbook of Pharmaceutical Controlled Release Technology, Marcel Dekker, Inc. New York, 2005; 751.
7. Santus, G. and Baker, W.R., Osmotic drug delivery: a review of the patent literature, J. Contr. Release, 1995; 35: 1-21.
8. Padma. V. D., Patil, G. P., and Dabholkar, R. D., Osmotic DDS. An Overview, Express PharmaPulse, special feature, 2003; 29: 36-38.
9. Wong P. S. L., P., Barclay, L., Deters, J. C., Theeuwes, F.; Osmotic device for administering certain drugs; US Patent, 1988; 4,765,989.
10. Theeuwes, F.; Elementary Osmotic Pump; J. Pharm. Sci, 1975; 64: 1987- 1991.
11. S. Rose, J.F. Nelson, A continuous long-term injector, Aust. J. Exp. Biol, 1955; 33: 415–420.
12. Alzet osmotic mini pump products/imp/exp, 1976.
13. Parma, N.S., and Vyas S.K., (Ed) N.K.jain, In: Advanced in controlled and novel drug delivery. CBS publisher, 28-29.
14. Higuchi. T. and Leeper, H.M.; Improved osmotic dispenser employing magnesium sulphate and magnesium chloride, U. S. patent, 1973; 3,760, 804.
15. Higuchi, T.; Osmotic dispenser with collapsible supply container, U.S. patent 3,760,805 (1973).
16. Higuchi, T. and Leeper, H.M.; Osmotic dispenser with means for dispensing active agent responsive to osmotic gradient, U.S. patent 3 ,995.63 1 (1976).

17. Theeuwes, F., Highuchi, T.; Osmotic dispensing device for releasing beneficial agent; US Patent, 1974; 3,845, 770.
18. Appel, L. E. and Zentner G. M.; Use of modified ethylcellulose lattices for microporous coating of osmotic tablets. Pharm. Res, 1991; 8(5): 600-604.
19. Jensen, J.L, Appel, L.E., Clair, J.H., Zentner, G.M.; variables that affect the mechanism of drug release from osmotic pumps coated with acrylate/methacrylate copolymer latexes. J. Pharm. Sci, 1995; 84: 530-533.
20. Baker, R.W.; Materials Used in Controlled Release Devices, In Controlled Release of Biologically Active Agents; John Wiley and sons, New York, 1987; 172.
21. Zentner, G.M., Rork, G.S., and Himmelstein, K.J.; Controlled porosity osmotic pump, U.S. Patent, 1990; 4, 968, 507.
22. Cortese, R., Theeuwes, F.; Simultaneous delivery of two drugs from unit delivery device, US Patent, 1982; 4, 327, 725.
23. Swanson, D. R., Barclay, B. L., Wong, P. S. L. and Theeuwes, F. Nifedipine gastrointestinal therapeutic system., Ameri. J. Med., Vol. 83, suppl 6B, 1987; 3-9.
24. Vyas, S.P. and Khar R.K., Controlled drug delivery. Concepts and Advances, 1st Edn., Vallabh Prakashan, New Delhi, 2002; 477-502.
25. Haslam, J.L., Rork, G.S., Controlled porosity osmotic pump, Nov.14, US Patent 4880631 (1989).
26. Thombre, A.G., Cardinal, J.R., DeNoto, A.R., and Gibbes, D.C., Asymmetric membrane capsules for osmotic drug delivery II: In vitro and in vivo drug release performance, J. Contr. Release, 1999; 57: 65-73.
27. Lin, Y. and Ho, H., Investigations on the drug releasing mechanism from an asymmetric membrane. coated capsule with an in situ formed delivery orifice, J. Contr. Release, 2003; 89: 57-69.
28. Baker, R.W.; Controlled release delivery system by an osmotic bursting mechanism, US Patent3,952,74 1 (1976).
29. http// www.expresspharmaonline.com / 20030828/ research01.html
30. Theeuwes, F., Wong, P.S.L., Burkoth, T.L. and Fox, D.A., Osmotic systems for colon-targeteddrug delivery, In: Bieck, P.R., (Eds)., Colonic drug Absorption and Metabolism, Marcel Dekker, Inc. New York, 1993; 137-158.
31. Liu, L., Ku, J., Khang, G., Lee, B., Rhee, J.M. and Lee, H.B., Nifedipine controlled deliveryby sandwiched osmotic system, J. Contr. Release, 2000; 68: 145-156.
32. Chen, D. L., and Xie J., Controlled release formulation for water insoluble drugs in which

a passageway is situ, April 7, US Patent 5736159 (1998).

33. Liu, L., Khang, G., Rhee, J.M. and Lee, H.B., Monolithic osmotic tablet system for nifedipine delivery, J. Contr. Release, 2000; 67: 309-322.
34. Pandey Shivanand, Viral Devmurari, Osmotic Pump Drug Delivery Devices: From Implant to Sandwiched Oral Therapeutic System Int. J. PharmTech Research, 2010; 2(1): 693–699.
35. Schultz, P. and Kleinebudde, P., A new multiparticulate delayed release system: Part 1: Dissolution properties and release mechanism, J. Contr. Release, 1997; 47: 181–89.
36. Padma. V. D., Patil, G. P., and Dabholkar, R. D., Osmotic DDS. An Overview, Express Pharma Pulse, special feature, 2003; 29: 36-38.
37. Vincent Malaterre, Joerg Ogorka, Nicoletta Loggia, Robert Gurny, Oral osmotically driven systems: 30 years of development and clinical use, European Journal of Pharmaceutics and Biopharmaceutics, 2009; 73: 311–323.
38. Patel, G. M. and Jayendra Patel. "Single Core Osmotic Pump (SCOP): Development of Single Layer Osmotic controlled release tablet for poorly soluble drug." (2012).
39. Shah, Nihar B. et al. "A Review on Osmotically Controlled Oral Drug Delivery Systems." (2012).
40. Keraliya, R. A., Patel, C., Patel, P., Keraliya, V., Soni, T. G., Patel, R. C., & Patel, M. M. (2012). Osmotic drug delivery system as a part of modified release dosage form. *ISRN pharmaceutics*, *2012;* 528079.
41. Manish Chawla, Shailesh Vishwanath BIRADAR, Mayur LOYA, Jayendrakumar Dasharathlal Patel, Akshay Virendra AGARWAL, Extended release osmotic dosage form comprising high methylphenidate hydrochloride load, US patent application number: US20180360817A1, 2016.
42. Jayendrakumar Patel, Shwetaben Patel, Major Obstacles in Technology Transfer of Nanomedicine from Conception to Commercialization, International Journal of Pharmaceutical Research and Applications, Volume 5, Issue 2, pp: 333-342, DOI: 10.35629/7781-0502333342.