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Osmotic Pump: A Reliable Drug Delivery System

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ABSTRACT

In a typical therapeutic regimen the drug dose and dosing interval are optimized to maintain drug concentration within the therapeutic window, thus ensuring efficacy while minimizing toxic effects. Controlled drug delivery systems offer spatial control over the drug release. Osmotic pumps are most promising systems for controlled drug delivery. Osmotic pump uses the basic principle of osmosis for release of drug(s). Osmotic pumps consist of an inner core containing drug and osmogens, coated with a semi permeable membrane. As the core absorbs water, it expands in volume, which pushes the drug solution out through the delivery ports. Osmotic pumps release drug at a rate that is independent of the pH and hydrodynamics of the dissolution medium. Various patents available for osmotic drug delivery system like Rose-Nelson pump, Higuchi-leeper pump, higuchi-theeuwes pump, elementary osmotic pump etc.

Keywords: Osmosis, Control drug delivery system, component of osmotic system, Osmotic pump

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INTRODUCTION

Conventional drug delivery systems have little control over the drug release and so effective concentration at the target site cannot be achieved. This kind of dosing pattern may result in unpredictable plasma concentrations. But oral controlled drug delivery dosage forms provide desired drug release pattern for longer period of time and so the rate and extent of drug absorption from oral controlled drug delivery formulations can be predicated. [1] But various conventional controlled release (CR) systems such as matrix or reservoir type may show bioavailability fluctuation because of change in gastric pH and hydrodynamic condition of body. Osmotic systems show drug release independent to gastric physiological factor as the release of drug from this type of system is guided by osmosis, which itself is independent of pH of environment. Osmotic drug delivery systems can be of various designs like implants, tablets etc.[2, 3] In this group of Control drug delivery system (CDDS) the release of drug molecule from the drug delivery system is activated by some physical, chemical, or biochemical processes.

Classifications

1. Physical mean

a. Osmotic pressure activated drug delivery system.
b. Hydrodynamic pressure activated drug delivery system
c. Vapor pressure activated drug delivery system
d. Mechanically activated drug delivery system
e. Magnetically activated drug delivery system
f. Sonophoresis activated drug delivery system
g. Ionotrophoresis activated drug delivery system
h. Hydration activated drug delivery system

2. Chemical means

a. pH activated drug delivery system.
b. Ion exchange drug delivery system.
c. Hydrolysis activated drug delivery system.

3. Biochemical means

a. Enzyme activated drug delivery system.
b. Biochemical activated drug delivery system. [4]

Osmotically Controlled Drug Delivery System (OCDDS) Osmotic devices are the most reliable controlled drug delivery systems (CDDS) and can be employed as oral drug delivery systems. Osmotic pressure is used as the driving force for these systems to release the drug in a

controlled manner. Osmotic pump tablet (OPT) generally consists of a core including the drug, an osmotic agent, other excipients and semi permeable membrane coat. [5]

What is osmosis?

Osmosis refers to the process of movement of solvent molecules from lower concentration to higher concentration across a semi permeable membrane. Osmosis is the phenomenon that makes controlled drug delivery a reality. Osmotic pressure created due to imbibitions of fluid from external environment into the dosage form regulates the delivery of drug from osmotic device. Rate of drug delivery from osmotic pump is directly proportional to the osmotic pressure developed due to imbibitions of fluids by osmogen. Osmotic pressure is a colligative property of a solution in which the magnitude of osmotic pressure of the solution is independent on the number of discrete entities of solute present in the solution. Hence the release rate of drugs from osmotic dispensing devices is dependent on the solubility and molecular weight and activity coefficient of the solute (osmogent). [6]

Principles of Osmosis

The first report of an osmotic effect dates to Abbenollet (1748). But Pfeffer obtained the first quantitative measurement in 1877. In Pfeffer experiment a membrane permeable to water but impermeable to sugar is used to separate a sugar solution from pure water. A flow of water then takes place into the sugar solution that cannot be halted until a pressure π is applied to the sugar solution. Pfeffer showed that this pressure, the osmotic pressure π of the sugar solution is directly proportional to the solution concentration and the absolute temperature. With in few years, Vant Hoff had shown the analogy between these results and ideal gas laws by the expression

$$\pi = \Phi\ c\ r\ t$$

Where Φ is the osmotic coefficient of the solution,
c is the molar concentration of sugar in the solution,
r is the gas constant
t is the absolute temperature.

Osmotic pressure for concentrated solution of soluble solutes commonly used in controlled release formulation are extremely high ranging from 30 atm for sodium phosphate up to 500 atm for a lactose-fructose mixture, as their osmotic pressure can produce high water flow across semi permeable membrane. The osmotic water flow through a membrane is given by the equation

$$dv\backslash dt = A\ Q\ \Delta\ \pi\backslash\ L$$

Where dv\dt is water flow across the membrane of area
A, thickness
L, and the permeability
Q in cm^2

Δ π is the osmotic pressure difference between the two solutions on either side of the membrane.

This equation is strictly for completely perm selective membrane that is membrane permeable to water but completely impermeable to osmotic agent. [7], [8]

ADVANTAGES

1. Easy to formulate and simple in operation.
2. Improve patient compliance with reduced frequency.
3. Prolonged therapeutic effect with uniform blood concentration.
4. They typically give a zero order release profile after an initial lag.
5. Deliveries may be delayed or pulsed if desired.
6. Drug release is independent of gastric pH and hydrodynamic condition.
7. They are well characterized and understood.
8. The release mechanisms are not dependent on drug.
9. A high degree of in-vitro and in-vivo correlation (IVIVC) is obtained in osmotic systems.
10. The rationale for this approach is that the presence of water in git is relatively constant, at least in terms of the amount required for activation and controlling osmotically base technologies.
11. Higher release rates are possible with osmotic systems compared with conventional diffusion-controlled drug delivery systems.
12. The release from osmotic systems is minimally affected by the presence of food in gastrointestinal tract.
13. The release rate of osmotic systems is highly predictable and can be programmed by modulating the release control parameters. [5] [9]

BASIC COMPONENT OF OSMOTIC SYSTEM

Drug

All drugs are not suitable candidate for osmotic system as prolong action medication .Drug with biological half-life > 12 hr e.g.: Diazepam and drug which have very short half life i.e. <1 hr e.g. Penicillin G, furosemide are not suitable candidate for osmotic controlled release. Drug which have biological half-life in between 1 – 6 hrs and which is used for prolonged cure of diseases are ideal applicant for osmotic systems. [10]

Drug having following characteristics are suitable for formulation

1. It should have short half-life
2. Prolonged release of drug should be desired.
3. It should be potent in nature.
4. Solubility of drug should not be very high or very low. [11]

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Osmotic agent

These are also known as osmogens or osmogents and are used to create osmotic pressure inside the system. When the solubility of drug is low then the drug will show zero order release but at a slow rate. To enhance the release rate osmotic agent is added in the formulation. Osmotic agent creates a very high osmotic pressure gradient inside the system and increases release rate of drug. [12] There are several osmotic agents which are used in osmotic system along with their osmotic pressure (Table 1) [13] [14].

Table No 1: Some of the commercially used osmotic agents along with their osmotic pressure

Sl. no.	Compound/ mixture	Osmotic pressure (atm)
1	Sodium chloride	356
2	Fructose	355
3	Potassium chloride	245
4	Sucrose	150
5	Xylitol	104
6	Sorbitol	84
7	Dextrose	82
8	Citric acid	69
9	Tartaric acid	67
10	Mannitol	38
11	Potassium sulphate	39
12	Lactose	23
13	Fumaric acid	10
14	Adipic acid	8
15	Potassium phosphate	105
16	Melanic acid	117
17	Lactose – Fructose	500
18	Dextrose – Fructose	450
19	Sucrose – Fructose	430
20	Mannitol – Fructose	415
21	Lactose - sucrose	250
22	Lactose – Dextrose	225
23	Mannitol – Dextrose	225
24	Dextrose – Sucrose	190
25	Mannitol - Sucrose	170
26	Mannitol - Lactose	130

27	Sodium phosphate Tribasic $12H_2O$	36
28	Sodium phosphate dibasic 7 H_2O	31
29	Sodium phosphate dibasic $12H_2O$	31
30	Sodium phosphate Dibasic anhydride	29
31	Sodium phosphate Monobasic .H_2O	28

Semi permeable Membrane

Since the membrane in osmotic systems is semi permeable in nature, any polymer that is permeable to water but impermeable to solute can be selected. [15] Cellulose acetate is a commonly employed semi permeable polymer for the preparation of osmotic pumps. It is available in different acetyl content grades. Particularly, acetyl content of 32% and 38% are widely used. Acetyl content is described by the degree of substitution (DS), i.e. t he average number of hydroxyl groups on the anhydroglucose unit of the polymer replaced by substituting group. Some of the polymers that can be used for above purpose include cellulose esters such as cellulose acetate, cellulose diacetate, cellulose triacetate, cellulose propionate, cellulose acetate butyrate, and cellulose ethers like ethyl cellulose. [16]

Ideal Property of Semi Permeable Membrane

The Semi Permeable Membrane must meet some performance criteria;

1. The material must possess sufficient wet strength (-105) and wet modulus so as to retain its dimensional integrity during the operational lifetime of the device.
2. The membrane exhibit sufficient water permeability so as to retain water flux rate in the desired range. The water vapor transmission rates can be used to estimate water flux rates.
3. The reflection coefficient and leakiness of the osmotic agent should approach the limiting value of unity. Unfortunately, polymer membranes that are more permeable to water are also, in general more permeable to the osmotic agent.
4. The membrane should also be biocompatible. [14]

Wicking agent

The wicking agents are those agents which help to increase the contact surface area of the drug with the incoming aqueous fluid. The use of the wicking agent help to enhance the rate of drug released from the orifice of the drug. The examples are colloidal silicon dioxide, PVP & Sodium laryl sulphate. [14]

Pore Forming Agents

The pore-forming agents cause the formation of micro porous membrane. The micro porous wall may be formed *in situ* by a pore-former by its leaching during the operation of the system. The pore-formers can be inorganic or organic and solid or liquid in nature. For example, alkaline metal salts such as sodium chloride, sodium bromide, potassium chloride, potassium sulphate, potassium phosphate etc., alkaline earth metals such as calcium chloride and calcium nitrate, carbohydrates such as sucrose, glucose, fructose, mannose, lactose, sorbitol, and mannitol and, diols and polyols such as poly hydric alcohols, polyethylene glycols and polyvinyl pyrrolidone can be used as pore forming agents. [17]

Coating solvents

The primary function of solvent system is to dissolved or dispersed the polymer and other additive and convey them to substrate surface. solvent used to prepare polymeric solution include inert inorganic and organic solvents that do not adversely harm the core ,wall and other material .the various types of solvents and their combinations are as follows: Methylene chloride, methanol, isopropyl alcohol, dichloromethane , ethyl acetate, acetone, carbon tetrachloride, cyclohexane, butyl alcohol, water etc and the mixture of solvents such as acetone-methanol(80:20), methylene chloride- methanol (79:21),acetone-ethanol(80:20), methylene chloride-methanol-water (75:22:3). [18]

Osmotic pump system

CLASSIFICATION OF OSMOTIC DRUG DELIVERY SYSTEM

Implantable

1. The Rose and Nelson Pump
2. Higuchi Leeper Pump
3. Higuchi Theuwes pump
4. Implantable Mini osmotic pump

Oral osmotic Pump

1. **Single chamber osmotic pump:**
   Elementary osmotic pump
2. **Multi chamber osmotic pump:**
   Push pull osmotic pump,
   Osmotic pump with non-expanding second chamber

Specific types

1. Controlled porosity osmotic pump,

2. Osmotic bursting osmotic pump,
3. Liquid OROS,
4. Delayed Delivery osmotic system
5. OROS-CT (colon targeting),
6. sandwiched oral therapeutic system,
7. Osmotic pump for insoluble drugs,
8. Monolithic osmotic system and OSMAT [9].

Implantable Pump

1. The Rose and Nelson Pump:

In, 1955, two Australian physiologists reported the first osmotic pump. They were interested in delivery of drug to the gut of sheep and cattle. The pump consisted of three chambers a drug chamber with an orifice, a salt chamber with elastic diaphragm containing excess solid salt, and a water chamber. A semipermiable membrane separates the drug and water chamber. The difference in osmotic pressure across the membrane moves water from the water chamber in to the salt chamber. (Figure 1) The volume of chamber increases because of this water flow, which distends the latex diaphragm separating the salt and drug chambers, thereby pumping drug out of the device [19].

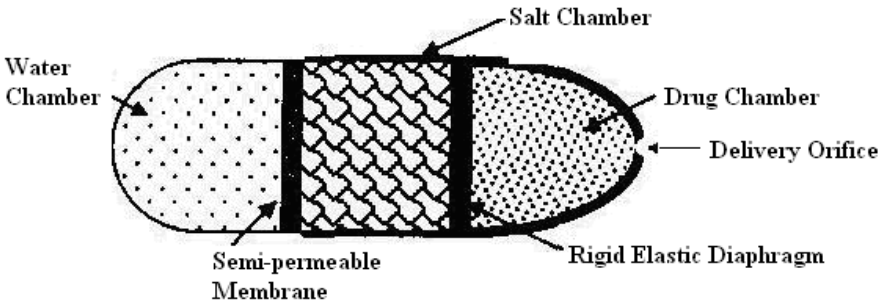

Figure 1. Rose Nelson Pump

2. Higuchi Leeper Pump

Higuchi Leeper pump is widely swallowed or implanted in the body of animal for delivery of antibiotic or growth hormones. Higuchi Leeper pump consist of rigid housing and semi permeable membrane. A layer of low melting waxy solid, such as microcrystalline paraffin wax is used in place of elastic diaphragm to separate the drug and osmotic chamber. (Figure 2) Recent modification in Higuchi-Leeper pump accommodated pulsatile drug delivery. The pulsatile release was achieved by the production of a critical pressure at which the delivery orifice opens and releases the drug. [20] Pulsatile delivery could be achieved by using Higuchi

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Leeper pump; such modifications are described and illustrated in Figure. The Pulsatile release of drug is achieved by drilling the orifice in elastic material that stretches under the osmotic pressure. Pulse release of drug is obtained after attaining a certain critical pressure, which causes the orifice to open. The pressure then reduces to cause orifice closing and the cycle repeats to provide drug delivery in a pulsatile fashion. The orifice should be small enough to be substantially closed when the threshold level of osmotic pressure is not present (Figure 3) [21].

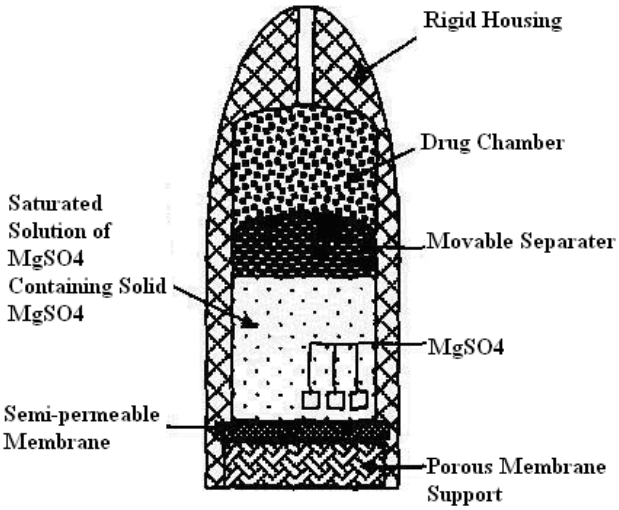

Figure 2. Higuchi Leeper Pump

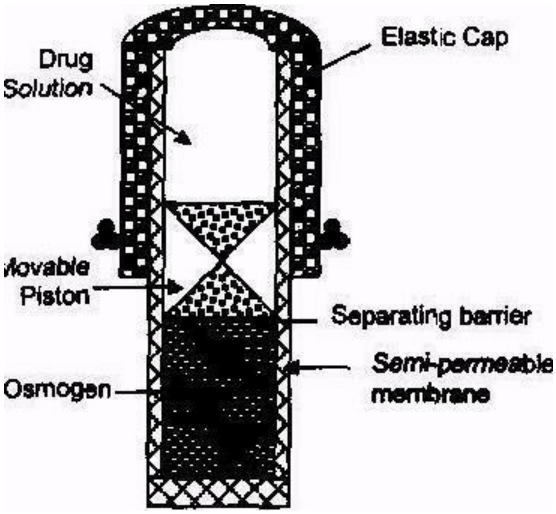

Figure 3. Pulsatile Release Osmotic Pump

3. Higuchi -Theeuwes pump

In the early 1970s, Higuchi and Theeuwes6 developed another, even simpler variant of the Rose-Nelson pump. As with the Higuchi- Leeper pump, water to activate the osmotic action of the pump is obtained from the surrounding environment. In the Higuchi-Theeuwes device,

however, the rigid housing is dispensed with and the membrane acts as the outer casing of the pump. (Figure 4) This membrane is quite sturdy and is strong enough to withstand the pumping pressure developed inside the device. The device is loaded with the desired drug prior to use. When the device is placed in an aqueous environment, 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. Most of the Higuchi-Theeuwes pumps use a dispersion of solid salt in a suitable carrier for the salt chamber of the device [22].

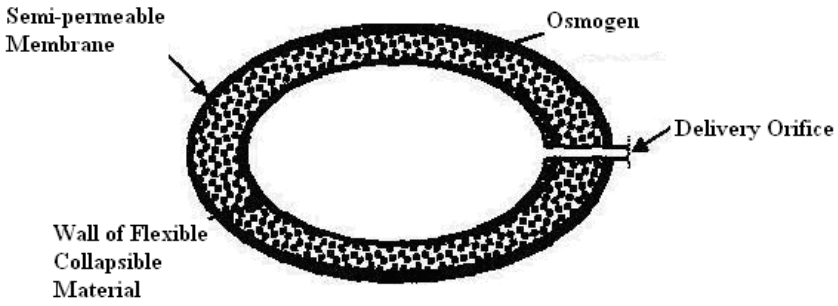

Figure 4. Higuchi -Theeuwes pump

4. Implantable Mini osmotic pump

Implantable Mini osmotic pump shown in figure 3 it is composed of three concentric layers-the drug reservoir, the osmotic sleeves and the rate controlling semi permeable membrane. The additional component called flow moderator is inserted into the body of the osmotic. The inner most compartment of drug reservoir which is surrounded by an osmotic sleeve, a cylinder containing high concentration of osmotic agent. The osmotic sleeve is covered by a semi permeable membrane when the system is placed in aqueous environment water enters the sleeve through semi permeable membrane, compresses the flexible drug reservoir and displaces the drug solution through the flow moderator. These pumps are available with variety of delivery rates between 0.25 to 10ml per hour and delivery duration between one day and four weeks [20].

Oral osmotic Pump

Single chamber osmotic pump

- Elementary osmotic pump

Elementary osmotic pump was invented by Theeuwes in 1974 and it essentially contains an active agent having a suitable osmotic pressure, it is fabricated as a tablet coated with semi permeable membrane, usually cellulose acetate. [23][14] A small orifice is drilled through the membrane coating. (Figure 5) When this coated tablet is exposed to an aqueous environment, the osmotic pressure of the soluble drug inside the tablet draws water through the semi

permeable coating and a saturated aqueous solution of drug is formed inside the device. The membrane is non-extensible and the increase in volume due to inhibition of water raises the hydrostatic pressure inside the tablet, eventually leading to flow of saturated solution of active agent out of the device through a small orifice [24].

The pump initially releases the drug at a rate given by equation;

$$dMt/dt = (dV/dt).\ Cs$$

Where,
dV/dt depicts the water flow into the tablet
Cs is the solubility of the agent inside the tablet.

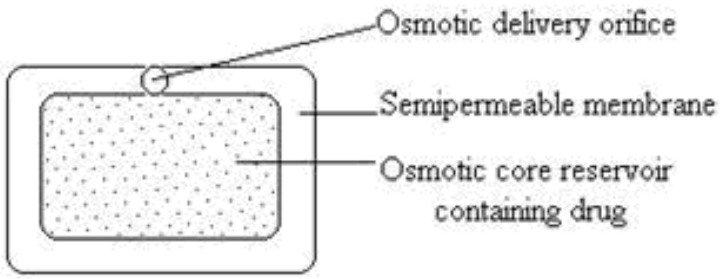

Figure 5. Elementary osmotic pump

Multi chamber osmotic pump

- **Push pull osmotic pump**

Push pull osmotic pump is a modified EOP. Through, which it is possible to deliver both poorly water-soluble and highly water soluble drugs at a constant rate. This system resembles a standard bilayer coated tablet. One layer (depict as the upper layer) contains drug in a formulation of polymeric, osmotic agent and other tablet excipients. This polymeric osmotic agent has the ability to form a suspension of drug in situ. When this tablet later imbibes water, the other layer contains osmotic and colouring agents, polymer and tablet excipients. These layers are formed and bonded together by tablet compression to form a single bilayer core. The tablet core is then coated with semi permeable membrane. 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 non-drug layer simultaneously attract water into that compartment, causing it to expand volumetrically and the expansion of non drug layer pushes the drug suspension out of the delivery orifice (Figure 6) [25][26].

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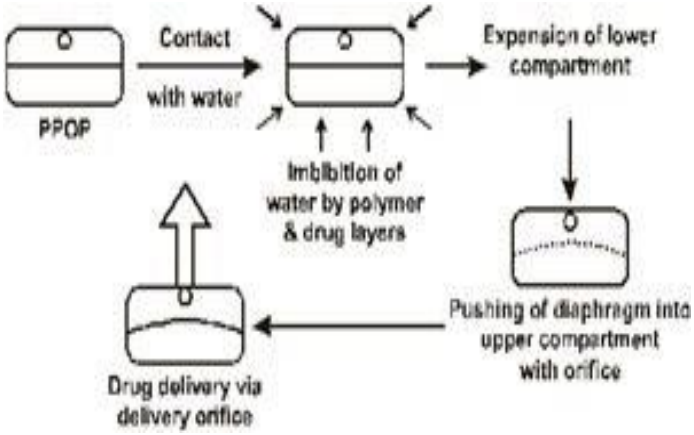

Figure 6. Push pull osmotic system

- **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 a saturated solution, irritation of GI tract is a risk. Example: The problem that leads to withdrawal of osmosin, the device consists of a normal drug containing porous tablet from which drug is released as a saturated solution. However before the drug can escape from the device it must pass through a second chamber. Water is also drawn osmotically into this chamber either because of osmotic pressure of drug solution or because the second chamber contain, water soluble diluents such as NaCl. This type of devices consist of two rigid chamber, the first chamber contains a biologically inert osmotic agent, such as sugar or a simple salt like sodium chloride, the second chamber contains the drug. In use water is drawn into both the chamber through the surrounding semi permeable membrane. The solution of osmotic agent formed in the first chamber then passes through the connecting hole to the drug chamber where it mixes with the drug solution before exiting through the micro porous membrane that form a part of wall surrounding the chamber. The device could be used to deliver relatively insoluble drugs [27].

Specific types

Controlled porosity osmotic pump

The pump can be made with single or multicompartment dosage form, in either form, the delivery system comprises a core with the drug surrounded by a membrane which has an asymmetric structure Membrane is permeable to water but impermeable to solute and insensitive pore forming additive dispersed throughout the wall. When exposed to water, low levels of water-soluble additive are leached from polymer materials that were permeable to water yet remained insoluble. Then resulting sponge like structure formed the controlled

porosity walls of interest and was substantially permeable to both water and dissolved drug agents.
The rate of flow dv/dt of water into the device can be represented as

$$dv / dt = Ak / h (Dp-DR)$$

Where k = Membrane permeability
A = Area of the membrane
Dp = Osmotic pressure difference
DR = Hydrostatic pressure difference

Osmotic bursting osmotic pump

In this system 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 [28].

Liquid OROS

Liquid OROS are designed to deliver drugs as liquid formulations and combine the benefits of extended release with high bioavailability. They are of three types: a) L OROS hard cap b) L OROS soft cap c) delayed liquid bolus delivery system. [29][30] L OROS hard cap or soft cap systems are designed to provide continuous drug delivery where as the L OROS delayed liquid bolus drug 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 rate controlling semi permeable membrane. The delivery orifice is drilled on the placebo layer end of the capsule shaped device. When the osmotic engine is expands, the placebo is released first, delaying release of the drug layer. Drug release can be delayed from I to 10 hour, depending on the permeability of the rate controlling membrane and thickness of the placebo layer [31].

Delayed Delivery osmotic system

This device consists of two chambers, the first contains the drug and an exit port, and the second contains an osmotic engine. A layer of wax like material separates the two section. To assemble the delivery device, the desired active agent is placed into one of the sections by manual or automated fill mechanism. The bilayer tablet with the osmotic engine is placed into a completed cap part of the capsule with the convex osmotic layer pointed in to the closed end of the cap and the barrier into the closed end of the cap and the barrier layer exposed towards the cap opening. The open end of the filled vessel is fitted inside the open end of the cap, and the two pieces are compressed together until the cap, osmotic bilayer tablet and vessel fit together tightly. As fluid is imbibed the housing of the dispensing device, the osmotic engine expand and exerts pressure on the slidable connected first and second wall sections. During the delay period the volume of reservoir containing the active agent is kept constant, therefore a negligible pressure gradient exists between the environment of use and interior of the

reservoir. As a result, the net flow of environmental fluid driven by the pressure enter the reservoir is minimal and consequently no agent is delivered for the period [32][33].

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 [14].

Sandwiched oral therapeutic system

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 agent's 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 [34].

Osmotic pump for insoluble drugs

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 substantially 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 micro porous 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 micro porous is coated at a moderate flow of unheated ambient air [35].

Monolithic osmotic system and OSMAT

It constitutes a simple dispersion of water-soluble agent in polymer matrix. When the system comes in contact in with the aqueous environment. Water imbibtion 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 then matrix in a serial fashion. However this system fails if more then 20 –30 volumes per liter of the active agents are

incorporated in to the device as above this level, significant contribution from the simple leaching of the substance take place [36].

Osmat It is a novel osmotically driven matrix system, which utilizes the hydrophilic polymers to swell, and gel in aqueous medium forming a semipermiable membrane in-situ releases from such a matrix system containing an osmogen could, therefore be modulated by the osmotic phenomenon. Osmat thus judiciously combines both matrix osmotic characteristics resulting in a quantum improvement in drug delivery from swellable matrix system. Osmat produces controlled drug release with adequate delivery rates in an agitation in dependent manner. Thus osmat represents simple, versatile, and easy to fabricate osmotically driven controlled drug delivery system based upon low cost technology [9].

EVALUATION PARAMETER OF OSMOTIC DRUG DELIVERY FORMULATION

Characterization of dosage form
Effect of osmotic agents
Swelling properties
Membrane stability and thickness
Orifice diameter and drug release
In-vitro drug release study. [37]

CONCLUSION

Osmotic pumps are the most reliable controlled drug delivery system. It uses osmotic pressure for controlled delivery of active agent. It allows targeted delivery of agents to virtually any tissue. Due to its small size it can be use in mice or young rats. It ensures around the clock exposure to test agent at predictable levels.

For these and other reasons future of osmotic drug delivery system will be excellent.

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