

Review on Osmotically Controlled Drug Delivery System

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ABSTRACT

Oral Osmotic Drug Delivery System is the new found delivery system of Novel Drug Delivery System. Oral Osmotic Drug Delivery System works on the principle of Osmosis and Osmotic Pressure for the pre-planned and correct delivery of the drugs into the biological systems. Being independent of the pH and physiological conditions, it provides an upper hand into delivery of drugs of various biological diversity. In this article a detailed discussion of Oral Osmotic Drug Delivery System it's components, classification, formulation aspects, evaluation techniques are described.

KEYWORD: *Osmosis, Osmotic pump, Components, Formulation Aspect*

How to cite this paper: Kanchan A. Lodhe | Vikram N. Sancheti "Review on Osmotically Controlled Drug Delivery System" Published in International Journal of Trend in Scientific Research and Development (ijtsrd), ISSN: 2456-6470, Volume-5 | Issue-1, December 2020, pp.961-965, URL: www.ijtsrd.com/papers/ijtsrd38144.pdf



IJTSRD38144

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INTRODUCTION

Osmotically controlled drug delivery system (OCDDS) is one of the most common and best drug delivery system that is done by using osmotic pressure as a driving force for the control delivery of active agent.[1] The drug are delivered through this system are not depending on pH Osmotic pump tablet (OPT). OPT consist of core including drug and osmotic agent, excipient and semipermeable membrane. The pharmaceutical agent can be delivered in controlled pattern over a long period by osmotic pressure. Osmotic pressure serves as an energy source. There has been increasing interest in development of osmotic device in past few decades. In 1975, the first oral osmotic pump was discovered which is called as Elementary osmotic pump (EOP). EOP was introduced by Theeuwes. The EOP is very simple to prepare and releases drug at zero order rate.

The EOP is suitable for delivery of water soluble drug, to overcome the limitation of EOP, two compartment, two layer push pull, monolithic osmotic delivery system and sandwiched osmotic delivery system were developed. Monolithic osmotic tablet system is especially suitable for water insoluble drug.[2]

Basic concept:

Osmosis: Osmosis refers to the process of movement of solvent molecule from lower concentration to higher concentration across a semi permeable membrane.[1]

Osmotic pressure: When the excess of solvent molecule passing in one direction creates a pressure, it is called as Osmotic Pressure. Osmotic pressure produced due to

permeation of fluid from external atmosphere into the dosage form to regulate the delivery of drug from osmotic device. Speed of drug release from osmotic pump is equivalent to the osmotic pressure which is developed due to permeation of fluid by an osmogen.[3]

Osmotic pressure is a colligative property, which depends on concentration of solute that contributes to osmotic pressure.[4]

Principle of osmosis: In 1748, Abbe Nollet reported the first osmotic effect. Later on, In 1877, Pfeffer performed an experiment on semipermeable membrane to separate sugar solution from pure water. He found that the osmotic pressure of sugar solution is directly proportional to the concentration and temperature. Afterword, In 1886, Vant Hoff state that the osmotic pressure is proportional to concentration and temperature. The relationship can be described by following equation:[4]

$$\pi = n2RT$$

Where,

π = Osmotic coefficient

$n2$ = Molar concentration

R= Gas constant

T= Absolute temperature.

It is based on the principle of osmotic pressure. Osmotic pressure is a colligative property, which depend on concentration of solute that contributes to osmotic pressure.

Solution of different concentration having the same solvent and solute system shows that osmotic pressure is proportionate to their concentration, thus a constant osmotic pressure and thereby a constant influx of water can be achieved by an osmotic drug delivery system. This results a constant zero order release of drug.[5]

Basic component:

- Drug
- Osmotic agent
- Polymer
- Binder
- Plasticizer
- Coating solvent
- Semipermeable membrane
- Osmotic pump

Drug: Both water soluble and water insoluble drug can be used in osmotic system for prolonged action. Drug candidate should possess short biological half life(1-6hr) [6]. Solubility of drug should not be very high or very low.[7] High potency should be required for chronic treatment, example: Antihypertensive, Antidiabetic, NSAID etc.

Osmotic agent: Osmotic agent is also known as osmogen. They are used to create osmotic pressure inside the system. Osmotic agent usually are ionic compound consisting of either inorganic salt such as sodium chloride and potassium chloride. [6,7]

Polymer: For making drug containing matrix core the polymer are used in osmotic system. According to drug nature, polymer should be selected, it may be hydrophilic polymer or hydrophobic polymer.[8] Hydrophilic polymer such as hydroxy ethyl cellulose, methylcellulose, HPMC and hydrophobic polymer such as ethyl cellulose and wax material can be used.[9] The selection of polymer is based on solubility of drug as well as amount of rate of drug release from the pump.[10] Swellable polymer are used for the pump containing moderately water-soluble drug. They enhance the hydrostatic pressure inside the pump due to their swelling nature. The non swellable polymer are used for highly water soluble drug[11]

Coating solvent:For making polymeric membrane,suitable solvent should be used. Various organic and inorganic solvent are used.[7]

Coating solvent should be nontoxic, should solubilize polymer completely and should not harm the core and other material, example; acetone, isopropyl alcohol, ethanol, methanol. The mixture of solvent such as acetone: methanol(80-20), acetone, ethanol (80-20), acetone : water(90-10), chloride-methanol-water (75-22-3).[12]

The ideal solvent should have following property:[13]

1. It should easily and completely dissolve.
2. Should be odourless, colourless and tasteless.
3. It should be non toxic and non irritant.
4. It should have rapid drying rate.

Wicking agent: Wicking agent helps to increase the contact surface area of the drug with the incoming aqueous fluid. It helps to enhance the rate of drug release from the orifice of the drug. Example: colloidal silicon dioxide, PVP, sodium

lauryl sulphate.[6] A wicking agent is either swellable or non swellable in nature.[14]The function of wicking agent is to carry water to surface inside the core of tablet thereby creating a channel of increased surface area. [10]

Plasticizer: In the formulation of osmotic system to coat the membrane, different type of plasticizer are used. It can change polymer visco elastic behaviour that may affect the polymeric film permeability, example: polyethylene glycol, ethylene glycol, monoacetate, tri ethyl citrate. [6,7]

Semipermeable membrane: Membrane used in osmotic system is semipermeable in nature. Any polymer that is permeable to water but impermeable to solute can be selected. Cellulose acetate (CA) is commonly used semipermeable polymer for the preparation of osmotic pump.[10]

Some of the polymer that can be used for above purpose include cellulose ester. Such as cellulose acetate, cellulose diacetate, cellulose triacetate, cellulose acetate butyrate and cellulose ether like ethyl cellulose.[15]Apart from cellulose derivative some other polymer such as agar acetate, amylose triacetate, polylactic derivative, poly glycolic acid can be used as semi permeable film forming material. [16] The permeability is an important criteria for selection of semipermeable polymer.[17]

Criteria for semipermeable membrane:[6]

1. It should have enough wet strength and water permeability.
2. It should biocompatible.
3. It should be adequately thick to withstand the pressure generated with the device.
4. It should be rigid and non swellable.

Classification: Oral Osmotic Drug Delivery System is classified into three types, they are-

- A. Single Chamber Osmotic Pump
- B. Multiple Chamber Osmotic Pump
- C. Modified Oral Osmotic Drug Delivery System

A. Single Chamber Osmotic Pump-

The main Single Chamber Osmotic Pump in use is Elementary Osmotic Pump (EOP). Elementary Osmotic Pump was developed by Theeuwes in 1975. EOP works on the most basic device and works on the principle of delivering the drug at a controlled rate by an osmotic process. EOP contains a drug of good aqueous solubility and can have an osmotic agent as well. It is surrounded by semi permeable membrane which is essentially rate controlling. The membrane is provided with an orifice for the controlled exposure of saturated solution of the drug which is the result of water imbibition by the fluid permeability of the membrane and the osmotic pressure of the compressed tablet when it is exposed to the aqueous environment. Conventional film coating technique are used to obtain semi permeable membranes which are made up of polymers like-Cellulose ethers, vinyl polymer, polyamides, polyesters. Delivery Orifice being the fourth component is obtained by the laser technique.

In EOP 60-80% of the drug is released at the constant rate, 30-60-minute lag time is usually observed due to system hydration. [17,18]

B. Multiple Chamber Osmotic Pumps-

There are two types of Multiple Chamber Osmotic Pumps that are available and these are-

1. Osmotic Pump with Non-Expanding Second Chamber
2. Push-Pull Osmotic Pump (PPOP)[18]

1. Osmotic Pump with Non-Expanding Second Chamber: This multi chamber device is particularly used for drugs with high occurrence of Gastro Intestinal irritation. Second chamber is used to dilute the drug solution or either it can be used to deliver two drugs at the same time. [18]

2. Push-Pull Osmotic Pump (PPOP): Drugs having extreme water solubility are often delivered using PPOP. PPOP delivers the drug using two compartments which are separated by elastic diaphragm. The drug is present in upper compartment while an osmotic agent is present in lower one. Drug is exposed to the external environment via a small delivery orifice. Delayed push-pull system, push-stick system and multiplayer push-pull system are some of the modifications of PPOP which are widely used. [23]

C. Modified OODDS:

1. Controlled Porosity Osmotic Pump (CPOP)
2. Osmotic Pump for Insoluble Drugs
3. Multiparticulate Delayed Release System
4. Monolithic Osmotic Pump
5. Colon targeted Oral Osmotic System
6. Sandwiched Osmotic Tablet (SOTS)
7. Liquid Oral Osmotic System (L-OROS)
8. Osmotic Matrix Tablet (OSMAT)

1. Controlled Porosity Osmotic Pump: The Coating membrane in CPOP usually contains water soluble additives like dimethyl sulfone, amino acids having pore size from 10A- 100um forming 5-95% pores which dissolve after exposure to aqueous environment resulting in formation of microporous membrane *in situ*. [18,19]

2. Osmotic Pump for Insoluble Drugs: An Elastic semipermeable membrane is used in this system to coat the osmogene. The Insoluble Drugs are mixed with these osmogen and are coated with semipermeable membrane. The two coatings when exposed to aqueous environment, water is taken up by the osmogene which results in drug delivery. [23]

3. Multi particulate Delayed Release System: It uses pellets consisting of drug and osmotic agents. The pellets are coated with semipermeable membrane. The pores are formed when the pellets are exposed to aqueous environment which results after water influx using osmotic pressure created. Drug is delivered through the pores.[3]

4. Monolithic Osmotic Pump: This system constitutes a simple dispersion of a water soluble agent in a polymeric matrix. Exposure to an aqueous environment results in water imbibition by active agents which in turn ruptures the matrix and thus the drug comes in contact with outside environment. It implies for the

system maintaining constant drug level in target tissue or cell.[2,18]

5. Colon targeted Oral Osmotic System: This system is used for targeted drug delivery into the colon. The hard gelatine capsules are used which dissolve after coming in contact with GI fluids. Push-Pull Osmotic system is used in this system. [23]

6. Sandwiched Osmotic Tablet: A polymeric push layer is used as a middle layer in this system which is sandwiched between the two drugs. After exposure to aqueous environment, the middle layer swells and the drug is released from the delivery orifices. [14,23]

7. Liquid Oral Osmotic System: L-OROS is of two types, L-OROS soft cap and L-OROS hard cap. In this system, osmotic layer gets reactivated when it comes in contact with the water which is permeated across the rate controlling membrane due when it is exposed to an aqueous environment. The activated osmotic layer creates hydrostatic pressure which ensures the drug delivery via drug orifices by liquid formation. [23]

8. Osmotic Matrix Tablet: OSMAT uses hydrophilic polymers to swell and gel in -aqueous medium forming a semipermeable *in situ*. Thus, OSMAT uses osmotic phenomenon to ensure drug release from the matrix system which contains osmogens.[1]

Formulation Aspect:

Release of drug from the osmotic pump depends on the following few factors:

1. Drug Solubility: Drug Solubility is one of the most important factors which decides the release of the drug as solubility is directly proportional to the release kinetics from the osmotic system. Drugs with moderate amount of solubility make good candidate for osmotic delivery than drugs with high or low solubilities.

Drug release with zero order kinetics can be given by the following equation-

$$F(z) = 1 - S/P$$

Where,

F(z) = fraction release of zero order

S= drug solubility in g/cm³

P= density of core tablet

Drug with density of unity and solubility less than 0.05 g / cm³ would release greater than or equals to 95 % by zero order kinetics.

Drug with density > 0.3 g / cm³ solubility would demonstrate with higher release rate > 70 % by zero order.[1,18]

2. Delivery Orifice: Most of the osmotic systems contain at least one delivery orifice for drug release. The size of the orifice has to be optimized as too small orifice can result into hydrostatic pressure and too large orifice may result into solute diffusion. The delivery orifice is made by either laser or mechanical drilling. [1,18]

3. **Coating Membrane:** A rate controlling membrane makes an important aspect in Osmotic System. Semipermeable polymers are preferred for osmotic systems having permeability for water but impermeability for solutes. Commonly used polymers are cellulose esters such as cellulose triacetate, cellulose proportionate, cellulose diacetate and cellulose acetate. Thickness of coating membrane is usually kept between 200-300um so as to withstand pressure in osmotic system. [1,18]

Evaluation of Oral Osmotic Drug Delivery Systems: [7,10]

Oral Osmotic Drug Delivery System is usually evaluated for the following-

1. **Visual Inspection-** Uniformity of coating, lustre, edge coverage and smoothness is evaluated by visual inspection.
2. **Orifice Diameter-** Pre calibrated ocular micro meter is used to determine orifice diameter of osmotic pump tablet.
3. **Coating Uniformity-** Weight, diameter and thickness of tablet is tested to determine uniformity of coating before and after the coating.
4. **Coat Weight and Thickness-** Standard analytical balance and screw gauge is used to determine coat weight and thickness.
5. **In Vitro Drug Release:** The in vitro delivery rate of drug is determined using vertically reciprocating shaker,

flow through cell apparatus and conventional USP dissolution apparatus I and II etc.

6. **In Vivo Evaluation-** Dogs are generally used for in vivo evaluation of oral osmotic drug delivery system for pH and motility. [1]

Advantages: [5,20,21,22]

1. ODDS give zero order release profile.
2. Enhanced bioavailability of drug
3. Release rate of drug is highly predictable and programmable
4. Delayed and pulsed delivery may be possible
5. Drug release is independent on gastric Ph
6. A high degree of *in vitro* and *in vivo* correlation (IVIVC) is obtained
7. Reduced side effect
8. Decrease dosing frequency
9. Improved patient compliance
10. Sustained and consistent blood level within therapeutic window.

Disadvantage:[6,21]

1. High cost
2. Retravel of therapy is not possible
3. Dose dumping
4. Whole size is critical
5. Rapid tolerance
6. Hypersensitivity reaction may occur.

List of some important patents based on osmotic drug delivery:[9,18,23]

Drug	System type	Us patent	Year
Indomethacin	Elementary osmotic pump	4265874	1981
Haloperidol	Elementary osmotic pump	4610686	1986
Chlorpheniramine	Elementary osmotic pump	4857330	1989
Nicotine	Elementary osmotic pump	5147654	1992
Nystatin	Elementary osmotic pump	5176493	1998
Levodopa	Elementary osmotic pump	5869096	1999
Procainamide HCL	Second expandable osmotic chamber	4331728	1982
Verapamil	Second expandable osmotic chamber	5156850	1992
Zafirlucast	Second expandable osmotic chamber	6224907	2001
Tandospirone	Multichamber osmotic system	5185158	1989
Glipizide	Multichamber osmotic system	5545413	1996
Captopril	Multichamber osmotic system	5976571	1999
Captopril	Multichamber osmotic system	6207191	2001
Nifedipine	Multichamber osmotic system	6352721	200

List of some commercially marketed oral osmotic drug delivery product: [9,18,23]

Product name	Active pharmaceutical ingredient	Design of osmotic pump
Acutrim	Phenylpropanolamine	Elementary osmotic pump
Alpress LP	Prazosin	Push-pull osmotic pump
Cardura XL	Doxazosin	Push-pull osmotic pump
Chronogesic TM	Sufentanil	Implantable osmotic system
Covera HS	Verapamil	Push-pull osmotic pump
Ditropan XL	Oxybutinin chloride	Push-pull osmotic pump
Dynacirc CR	Isradipine	Push-pull osmotic pump
Efidac 24	Pseudoephedrine	Elementary osmotic pump
Efidac 24	Chlorpheniramine meleate	Elementary osmotic pump
Glucotrol XL	Glipizide	Push-pull osmotic pump
Invega	Paliperdone	Push-pull osmotic pump
Minipress XL	Prozocine	Elementary osmotic pump
Procardia XL	Nifedipine	Push-pull osmotic pump
Sudafed 24	Pseudoephedrine	Elementary osmotic pump
Viadur	Leuprolide acetate	Implantable osmotic system
Volmax	Albutenol	Elementary osmotic pump

Conclusion-

OODDS use the principle of Osmosis as a driving force for drug delivery. OODDS have come a long way in last 25 years starting from a research tool to be actually used for drug delivery in the biological systems. The various advantages of OODDS such as being independent of pH system, physiological conditions like hydrodynamic forces and drug delivery at zero order rate. It promises the delivery of various diversified drugs by modulating various formulation. This system should be long lasting, effective and safe. This delivery system are highly acceptable and technique is interesting as well fruitful in the field of drug.

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