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A REVIEW ON OSMOTICALLY CONTROLLED DRUG DELIVERY SYSTEM

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ABSTRACT

This paper reviews constructed drug delivery systems applying osmotic principles for controlled drug release from the formulation. Osmotic devices which are tablets coated with walls of controlled porosity are the most promising strategy based systems for controlled drug delivery. In contrast to common tablets, these pumps provide constant (zero order) drug release rate. When these systems are exposed to water, low levels of water soluble additive is leached from polymeric material i.e. semipermeable membrane and drug releases in a controlled manner over an extended period of time. The main clinical benefits of oral osmotic drug delivery system are their ability to improve treatment tolerability and patient compliance. These advantages are mainly driven by the capacity to deliver drugs in a sustained manner, independent of the drug chemical properties, of the patient's physiological factors or following food intake. This review brings out the theoretical concept of drug delivery systems, osmosis, principle of osmosis, historical background, advantages and disadvantages of the delivery system, basic component of osmotic drug delivery, classification of osmotic system, factors affecting the drug delivery system, conclusion and marketed products.

KEYWORDS: Osmotic drug delivery system, Osmosis, Semipermeable membrane, Control drug delivery system, component of osmotic system.

INTRODUCTION

Conventional drug delivery systems have slight control over their drug release and almost no control over the effective concentration at the target site. This kind of dosing pattern may result in constantly changing, unpredictable plasma concentrations. Drugs can be delivered in a controlled pattern over a long period of time by the controlled or modified release drug delivery systems. They include dosage forms for oral and transdermal administration as well as injectable and implantable systems. For most of drugs, oral route remains as the most acceptable route of administration. Certain molecules may have low oral bioavailability because of solubility or permeability limitations. Development of an extended release dosage form also requires reasonable absorption throughout the gastro-intestinal tract (GIT). Among the available techniques to improve the bioavailability of these drugs fabrication of bioavailability of these drugs fabrication of osmotic drug delivery system is the most appropriate one. Osmotic drug delivery systems release the drug with the zero order kinetics which does not depend on the initial concentration and the physiological factors of GIT.

Osmosis

Osmosis refers to the process of movement of solvent molecules from lower concentration to higher concentration across a semi permeable membrane. Osmotic drug delivery system is the most appropriate one. Osmotic drug delivery systems release the drug with the zero order kinetics which does not depend on the initial concentration and the physiological factors of GIT.

Osmotic pressure

Osmotic pressure is a colligative property of a solution in which the magnitude of osmotic pressure of the solution is independent on the number of discrete entities of solute present in the solution. Osmotic pressure created due to imbibitions of fluid from external environment into the dosage form regulates the delivery of drug from osmotic device. Rate of drug delivery from osmotic pump is directly proportional to the osmotic pressure developed due to imbibitions of fluids by osmogen.

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. Within few years, Vant Hoff had shown the analogy between these results and ideal gas laws by the expression

$$\pi = Ø\ c\ RT$$

Where, p = Osmotic pressure,

π = osmotic coefficient,

c = molar concentration,

R = gas constant,

T = Absolute temperature.

Osmotic pressure is a colligative property, which depends on concentration of solute that contributes to osmotic pressure. Solutions of different concentrations having the same solute and solvent system exhibit an osmotic pressure proportional to their concentrations. Thus a constant osmotic pressure, and thereby a constant influx of water can be achieved by an osmotic delivery system that results in a constant zero order release rate of drug. Osmotic pressure for concentrated solution of soluble solutes commonly used in controlled release formulation are extremely high ranging from 30 atm for sodium phosphate up to 500 atm for a lactose-fructose mixture, as their osmotic pressure can produce high water flow across semi permeable membrane. The osmotic water flow through a membrane is given by the equation;

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

Where,

dv\dt = water flow across the membrane of area A in cm2,

L = thickness,

Q = permeability and

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

This equation is strictly for completely perm selective membrane that is membrane permeable to water but completely impermeable to osmotic agent.

HISTORICAL BACKGROUND

About 75 years after discovery of the osmosis principle, it was first used in the design of drug delivery systems6. Rose and Nelson, the Australian scientists, were initiators of osmotic drug

delivery. In 1955, they developed an implantable pump, which consisted of three chambers: a drug chamber, a salt chamber contains excess solid salt, and a water chamber. The drug and water chambers are separated by rigid semipermeable membrane. The difference in osmotic pressure across the membrane moves water from the water chamber into the salt chamber. The volume of the salt chamber increases because of this water flow, which distends the latex diaphragm separating the salt and drug chambers, thereby pumping drug out of the device. The design and mechanism of this pump is comparable to modern push-pull osmotic pump. The major disadvantage of this pump was the water chamber, which must be charged before use of the pump. The pumping rate of this push-pull pump is given by the equation;

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

In general, this equation, with or without some modifications, applies to all other type of osmotic systems. Several simplifications in Rose-Nelson pump were made by Alza Corporation in early 1970s. The Higuchi-Leeper pump is modified version of Rose Nelson pump. It has no water chamber and the device is activated by water imbibed from the surrounding environment. The pump is activated when it is swallowed or implanted in the body. This pump consists of a rigid housing, and the semipermeable membrane is supported on a perforated frame. It has a salt chamber containing a fluid solution with excess solid salt. Recent modification in Higuchi-Leeper pump accommodated pulsatile drug delivery. The pulsatile release was achieved by the production of a critical pressure at which the delivery orifice opens and releases the drug7.Further simplified variant of Rose-Nelson pump was developed by Higuchi and Theeuwes. This pump comprises a rigid, rate controlling outer semipermeable membrane surrounding a solid layer of salt coated on the inside by an elastic diaphragm and on the outside by the membrane. In use, water is osmotically drawn by the salt chamber, forcing drug from the drug chamber.

ADVANTAGES & DISADVANTAGES OF OSMOTIC CONTROLLED DRUG DELIVERY SYSTEMS

Advantages

- They typically give a zero order release profile after an initial lag.
- Deliveries may be delayed or pulsed if desired.
- Drug release is independent of gastric pH and hydrodynamic condition.
- They are well characterized and understood.
- The release mechanisms are not dependent on drug.

- A high degree of *in-vitro* and *in-vivo* correlation (*ivivc*) is obtained in osmotic systems.
- Higher release rates are possible with osmotic systems compared with conventional diffusion controlled drug delivery systems.
- The release from osmotic systems is minimally affected by the presence of food in gastrointestinal tract.
- The release rate of osmotic systems is highly predictable and can be programmed by modulating the release control parameters.
- The delivery rate of zero-order is achievable with osmotic systems

Disadvantages

- Special equipment is required for making an orifice in the system.
- It may cause irritation or ulcer due to release of saturated solution of drug
- Dose dumping
- Retrieval therapy is not possible in the case of unexpected adverse events.
- Expensive
- If the coating process is not well controlled there is a risk of film defects, which results in dose dumping
- Size hole is critical

BASIC COMPONENTS OF OSMOTIC SYSTEMS:

Drug

Which have short biological half-life and which is used for prolonged treatment are ideal candidate for osmotic systems. Various drug candidates such as Diltiazem HCl, Carbamazepine, Metoprolol, Oxprenolol, Nifedipine, Glipizide etc. are formulated as osmotic delivery.

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.

Semipermeable membrane

An important part of the osmotic drug delivery system is the semipermeable membrane housing. Therefore, the polymeric membrane selection is key to the osmotic delivery

formulation. The membrane should possess certain characteristics, such as impermeability to the passage of drug and other ingredients present in the compartments. The membrane should be inert and maintain its dimensional integrity to provide a constant osmotic driving force during drug delivery. Any polymer that is permeable to water but impermeable to solute can be used as a coating material in osmotic devices e.g. Cellulose esters like cellulose acetate, cellulose acetate butyrate, cellulose triacetate and ethyl cellulose and Eudragits.

Osmotic agent

Osmotic agents maintain a concentration gradient across the membrane. They also generate a driving force for the uptake of water and assist in maintaining drug uniformity in the hydrated formulation. Osmotic components usually are ionic compounds consisting of either inorganic salts or hydrophilic polymers. Osmotic agents can be any salt such as sodium chloride, potassium chloride, or sulfates of sodium or potassium and lithium. Additionally, sugars such as glucose, sorbitol, or sucrose or inorganic salts of carbohydrates can act as osmotic agents. The polymers may be formulated along with poly(cellulose), osmotic solutes, or colorants such as ferric oxide. Swellable polymers such as poly(alkylene oxide), poly (ethylene oxide), and poly (alkalicarboxymethylcellulose) are also included in the push layer of certain osmotic systems. Further, hydrogels such as Carbopol (acidic carboxypolymer), Cyanamer (polyacrylamides), and Aqua-Keeps (acrylate polymer polysaccharides composed of condensed glucose units such as diester cross-linked polygluran) may be used.

Flux regulators

Delivery systems can be designed to regulate the permeability of the fluid by incorporating flux regulating agents in the layer. Hydrophilic substances such as polyethethylene glycols (300 to 6000 Da), polyhydric alcohols, polyalkylene glycols, and the like improve the flux, whereas hydrophobic materials such as phthalates substituted with an alkyl or alkoxy (e.g., diethyl phthalate or dimethoxy ethylphthalate) tend to decrease the flux. Insoluble salts or insoluble oxides, which are substantially water-impermeable materials, also can be used for this purpose.

Wicking agent

A wicking agent is defined as a material with the ability to draw water into the porous network of a delivery device. A wicking agent is of either swellable or non-swellable nature. They are characterized by having the ability to undergo physisorption with water. Physisorption is a form of absorption in which the solvent molecules can loosely adhere to

surfaces of the wicking agent via Vander Waals interactions between the surface of the wicking agent and the adsorbed molecule. The function of the wicking agent is to carry water to surfaces inside the core of the tablet, thereby creating channels or a network of increased surface area. Materials, which suitably for act as wicking agents include colloidal silicon dioxide, kaolin, titanium dioxide, alumina, niacinamide, sodium lauryl sulphate (SLS), low molecular weight poly vinyl pyrrolidone (PVP), m-pyrol, bentonite, magnesium aluminium silicate, polyester and polyethylene.

Pore forming agent

These agents are particularly used in the pumps developed for poorly water soluble drug and in the development of controlled porosity or multiparticulate osmotic pumps. These poreforming agents cause the formation of microporous membrane. The microporous 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, mannitol and, diols and polyols such as poly hydric alcohols and polyvinyl pyrrolidone can be used as pore forming agents.

Coating solvent

Solvents suitable for making polymeric solution that is used for manufacturing the wall of the osmotic device include inert inorganic and organic solvents that do not adversely harm the core, wall and other materials. The typical solvents include methylene chloride, acetone, methanol, ethanol, isopropyl alcohal, butyl alcohal, ethyl acetate, cyclohexane, carbon tetrachloride, water etc. The mixtures of solvents such as acetone-methanol (80:20), acetone-ethanol (80:20), acetone-water (90:10), methylene chloride-methanol (79:21), methylene chloride-methanol-water (75:22:3) etc. can be used.

Plasticizers

Different types and amount of plasticizers used in coating membrane also have a significant importance in the formulation of osmotic systems. They can change visco-elastic behavior of polymers and these changes may affect the permeability of the polymeric films. Some of the plasticizers used are as below:

- Polyethylene glycols

- Ethylene glycol monoacetate; and diacetate- for low permeability
- Tri ethyl citrate
- Diethyl tartarate or Diacetin- for more permeable films.

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.

KEY PARAMETERS THAT INFLUENCE THE DESIGN OF OSMOTIC CONTROLLED DRUG DELIVERY SYSTEMS

Orifice size

To achieve an optimal zero-order delivery profile, the cross-sectional area of the orifice must be smaller than a maximum size to minimize drug delivery by diffusion through the orifice. Furthermore, the area must be sufficiently large, above a minimum size to minimize hydrostatic pressure buildup in the system. Otherwise, the hydrostatic pressure can deform

the membrane and affect the zero-order delivery rate. Therefore, the cross-sectional area of the orifice should be maintained between the minimum and maximum values. Methods to create a delivery orifice in the osmotic tablet coating are:

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

Solubility

The release rate depends on the solubility of the solute inside the drug delivery system. Therefore, drugs should have sufficient solubility to be delivered by osmotic delivery. In the case of low solubility compounds, several alternate strategies may be employed. Broadly, the approaches can be divided into two categories. First, swellable polymers can be added that result in the delivery of poorly soluble drugs in the form of a suspension. Second, the drug solubility can be modified employing different methods such as co compression of the drug with other excipients, which improve the solubility. For example, cyclodextrin can be included in the formulation to enhance drug solubility. Additionally, alternative salt forms of the drug can be employed to modulate solubility to a reasonable level. In one case, the solubility of oxprenolol is decreased by preparing its succinate salt so that a reduced saturation concentration is maintained.

Osmotic pressure

The osmotic pressure π directly affects the release rate. To achieve a zero-order release rate, it is essential to keep π constant by maintaining a saturated solute solution. Many times, the osmotic pressure generated by the saturated drug solution may not be sufficient to achieve the required driving force. In this case, other osmotic agents are added that enhance osmotic pressure. For example, addition of bicarbonate salt not only provides the necessary osmotic gradient but also prevents clogging of the orifice by precipitated drug by producing an effervescent action in acidic media.

Semipermeable membrane

Since the semipermeable membrane is permeable to water and not to ions, the release rate is essentially independent of the pH of the environment. Additionally, the drug dissolution process takes place inside the delivery system, completely separated from the environment.

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.

Marketed Products

Trade Name	Active ingredient	Design System
Alpress LP	Prazosin	Push –Pull
Acutrim	Phenylpropanolamine	Elementary pump
Cardura XL	Doxazosin	Push –Pull with time delay
Covera HS	Verapamil	Push –Pull
Ditropan XL	Oxybutinin chloride	Push –Pull
Dynacirc CR	Isradipine	Push –Pull
Glucotrol XL	Glipizide	Push –Pull
Minipress XL	Prazocine	Elementary Pump
Procardia XL	Nifedipine	Push –Pull
Sudafed 24	Pseudoephedrine	Elementary Pump

CONCLUSIONS

In osmotic delivery systems, osmotic pressure provides the driving force for drug release. Increasing pressure inside the dosage form from water incursion causes the drug to release from the system. The major advantages include precise control of zero-order or other patterned release over an extended time period—consistent release rates can be achieved irrespective of the environmental factors at the delivery site. Controlled delivery via osmotic systems also may reduce the side-effect profile by moderating the blood plasma peaks typical of conventional (e.g., instant release) dosage forms. Moreover, since efficacious plasma levels are maintained longer in osmotic systems, avoidance of trough plasma levels over the dosing interval is possible. However, a complex manufacturing process and higher cost compared with conventional dosage forms limit their use.

Although not all drugs available for treating different diseases require such precise release rates, once-daily formulations based on osmotic principles are playing an increasingly important role in improving patient compliance. Therefore, most of the currently marketed products are based on drugs used in long-term therapies for diabetes, hypertension, attention-deficit disorder, and other chronic disease states. Besides oral osmotic delivery systems, implants that work on osmotic principles are promising for delivery of a wide variety of molecules with a precise rate over a long period of time. Further, with the discovery of newer and potent drugs by the biotechnology industry, the need to deliver such compounds at a precise rate certainly will pave the way for osmotic delivery systems to play an increasingly important role in drug delivery.

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