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Osmotic Drug Delivery System: A Review

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ABSTRACT

Osmotic drug delivery uses the osmotic pressure level for controlled delivery of drugs by using osmogens. Osmotic systems for controlled drug-delivery applications are well established, both in human pharmaceuticals and in veterinary medicine. The process of osmosis that can control the drug delivery system. Osmotic pressure created from external environment into the dosage form regulates the delivery of drug from osmotic device. Osmotic pumps are promising systems for controlled drug delivery. The systems are used for oral administration and implantation. Osmotic pumps consist of an inner core containing drug and coated with a semi permeable membrane.

Keywords: Osmosis, Osmotic drug delivery system, Osmotic pump.

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INTRODUCTION

Drug delivery System ;[1-3]

Drug delivery is refer to the approaches, formulations, technologies, and systems for transporting the compound in the body as needed to safely achieve its desired therapeutic effect. It may be involve scientific site-targeting within the body or it might involve facilitating systemic pharmacokinetics in any case, it is typically concerned with both quantity and duration of drug presence. Drug delivery is often approached via a drug's chemical formulation, but it may also involve medical devices or drug-device combination products.

Drug delivery of the technologies modifies drug release profile absorption, distribution and elimination for the benefit of improving product efficacy and safety as well as patient convenience and compliance. Drug release is from diffusion, degradation, swelling, and affinity based mechanisms.

Novel drug delivery system;

In the novel drug delivery systems (NDDS), there are various novel carriers which have advantage over conventional dosage forms. Conventional dosage forms show high dose and low availability, in-stability, first pass effect, plasma drug level fluctuations and rapid release of the drug.

Novel drug delivery system is one of the important tool of developed drug markets in pharmaceutical industry. Novel drug delivery system can minimize the problems by enhancing efficacy, safety, patient compliance and product shelf life.[4]

Osmotic drug delivery System:

Osmotic drug delivery system has come a long way since Australian physiologists Rose and Nelson developed an implantable pump in 1955. Osmotic drug delivery system used to the osmotic pressure for controlled delivery of drugs by using osmogens (for up to 10 – 16 hrs). Osmotic systems for controlled drug-delivery applications are well established, both in human pharmaceuticals and in veterinary medicine.[5] oral drug delivery systems are known to provide the immediate release of drug, in which one cannot control the release of the drug and cannot maintain effective concentration at the target site for longer time.6few one compartment and two-compartment osmotic systems have been reviewed previously.[7-10]

Osmotically controlled drug delivery system delivery the drug in a large extent and the delivery nature is independent of the physiological factors of the gastrointestinal tract and these

systems can be utilized for systemic as well as targeted delivery of drugs. Osmotically controlled oral drug delivery systems utilize osmotic pressure for controlled delivery of active agents.[11]

Osmotic Pump Controlled Release Preparation is a novel drug delivery system with permanently drug delivery rate as characteristic and controlled with the osmotic pressure difference between inside and outside of the semi permeable membrane as drug delivery power.[12]

Osmosis can be defined as the spontaneous movement of a solvent from a solution of lower solute concentration to a solution of higher solute concentration through an ideal semi permeable membrane, which is permeable only to the solvent but should not permeable to the solute. The pressure applied to the higher concentration side to inhibit solvent flow is called the osmotic pressure[13].

OSMOSIS:

Process of movement of the solvent from the lower concentration of solution to the higher concentration of the solution through the semi permeable membrane. Osmosis is the process of control the drug delivery system. Osmotic pressure created due to imbibing 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 imbibing of fluids by osmogen. Osmotic pressure is a colligative properties 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 distribute devices is dependent on the solubility and molecular weight and activity coefficient of the solute.[14]

Principle of Osmosis;

The first report of an osmotic effect dates to Abbenollet (1748). But Pfeffer obtained the first quantitative measurement in 1877. In the 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 stop 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 complete temperature. Within 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 = osmotic coefficient of the solution,

c = molar concentration of sugar in the solution,

r= gas constant,

t = 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

$$Dv/dt = A Q \Delta \pi / L$$

Where

dv\dt =water flow across the membrane of area

A= thickness L, and the permeability

Q in cm2 **,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.[15]

Instrumentation

Types of Osmotic Pumps;

Osmotic pump;

Osmotic pumps are most good systems for controlled drug delivery. These systems are used to oral administration. Osmotic pumps consist of an inner core containing drug coated with a semi permeable membrane.

Rose-Nelson Pump*;*

Rose and Nelson, the Australian scientists, were initiators of osmotic drug delivery. In 1955, they developed an implantable pump for the delivery of drugs to the sheep and cattle gut.

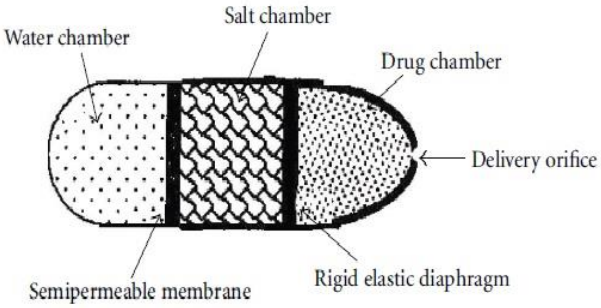

Figure 1: Rose Nelson Pump.

A semi-permeable membrane separate the salt from water chamber. The movement of water from the water chamber towards salt chamber is affcet by difference in osmotic pressure across the membrane. The volume of salt chamber increases due to water flow, which distends the latex diaphragm dividing the salt and drug chambers eventually, the drug is pumped out of the device.

The kinetics of pumping from Rose Nelson pump is given by the following equation:

$$dMt/dt = (dV/dt).C,$$

where dMt/dt is the drug release rate, dV/dt is the volume flow of water into the salt chamber, and C represents the concentration of drug in the drug chamber.

The major problem connect with Rose-Nelson pumps was that the osmotic action began whenever water came in contact with the semi permeable membrane. This needed pumps to be stored empty and water to be loaded prior to use.

$$dMt/dt = A\Theta\Delta\pi\ C/l$$

where, A is the area of semi permeable membrane, Δπ is the osmotic pressure gradient, θ is the permeability of semi-permeable membrane, and l is the thickness of semi-permeable membrane. These basic equations are relevant to the osmotically driven controlled drug delivery devices. The

saturated salt solution created a high osmotic pressure compare to that pressure required for pumping the suspension of active agent. Therefore, the rate of water entering into the salt chamber remain constant as long as sufficient solid salt is present in die salt chamber to maintain a saturated solution and thereby a constant osmotic pressure driving force is generated. major problem associate with Rose-Nelson pumps was that the osmotic action began whenever water came in contact with the semi-permeable membrane. This pumps to be stored empty and water to be loaded prior to use[16].

Higuchi-Leeper Osmotic Pump*;*

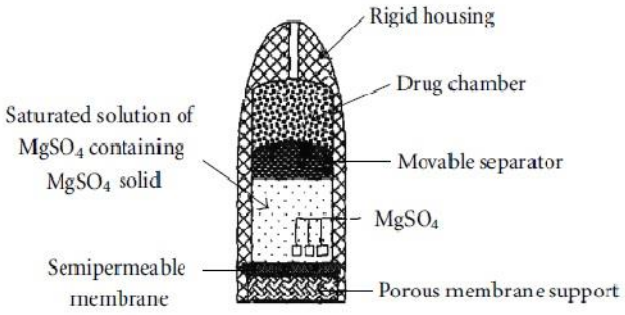

Figure 2: Higuchi-Leeper osmotic pump

This variation allows the device to be prepare loaded with drug and can be stored for long prior to use. Higuchi-Leeper pumps contain a rigid housing and a semi-permeable membrane supported on a perforated frame; a salt chamber containing a fluid solution with an excess of solid salt is usually present in this type of pump. Upon administration/implantation, surrounding biological fluid penetrates into the device through porous and semi-permeable membrane and dissolves the MgSO4, creating osmotic pressure inside the device that pushes movable separator toward the drug chamber to remove drug outside the device. It is widely employed for the veterinary use. This type of pump is insert in body of an animal for delivery of antibiotics or growth hormones to animals.[17]

Pulsatile delivery could be achieved by using Higuch-Leeper pump;

The Pulsatile release of drug is achieved by drilling the orifice in elastic material that elastic under the osmotic pressure. Pulse release of drug is obtained after attained 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.[18]

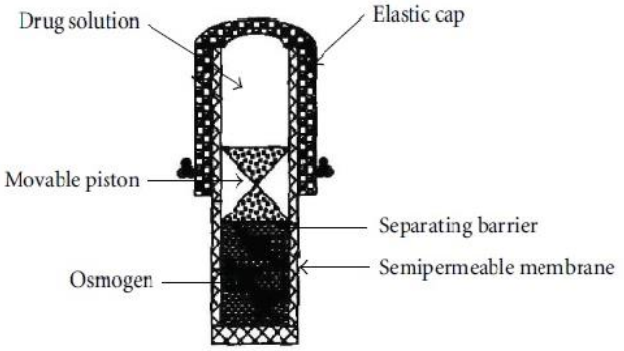

Figure 3: Pulsatile release osmotic pump

Higuchi-Theeuwes Osmotic Pump;

In this device, the rigid housing consisted of a semi-permeable membrane. This membrane is strong enough to with stand the pumping pressure developed inside the device due to of water. The drug is loaded in the device only prior to its application, which extends advantage for storage of the device for longer duration. The release of the drug from the device is governed by the salt used in the salt chamber and the permeability characteristics of the outer membrane.[19]

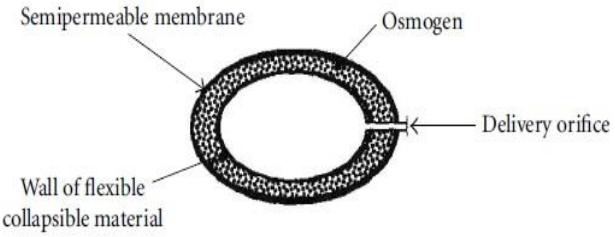

Figure 4: Higuchi Theeuwes Pump.

Elementary Osmotic Pump (EOP*);*

The Rose-Nelson pump was further simplified in the form of elementary osmotic pump which made osmotic delivery as a major method of achieve controlled drug release[20-21]. Elementary osmotic pump shown was invented by essentially contains an active agent having a suitable osmotic pressure; it is fabricated as a tablet coated with semi permeable membrane, usually cellulose acetate.[22-23]

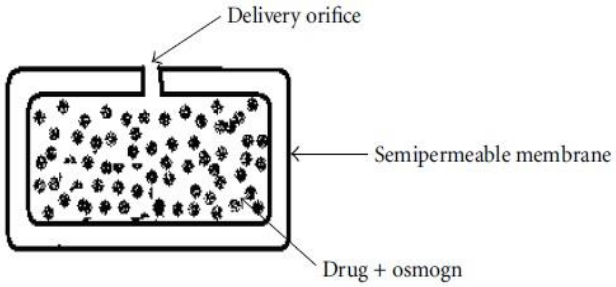

Figure 5: The elementary osmotic pump.

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

$$dMt/dt=(dV/dt).cs$$

where ***dV/dt*** depicts the water flow into the tablet and ***Cs*** is the solubility of the agent inside the tablet.

Push-Pull Osmotic Pump (PPOP);

Push-pull osmotic pump is delivered both poorly water soluble and highly water soluble drugs at a constant rate. This system resembles a standard bilayer coated tablet contains drug in a formulation of polymeric, osmotic agent, and other tablet excipients. This polymeric osmotic agent has the capacity 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.[24-25]

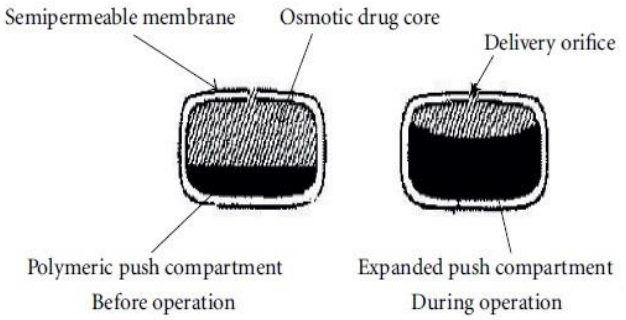

Figure 6: The push-pull osmotic pump (PPOP).

Controlled Porosity Osmotic Pump (CPOP);

Figure 6 represents the controlled porosity osmotic pump (CPOP). It is an osmotic tablet wherein the delivery orifices (holes) are formed in situ through leaching of water soluble pore-forming agents incorporated in semi-permeable membrane (SPM) (e.g., urea, nicotinamide, sorbitol, etc.). Drug release rate from CPOP depends on various factors like coating thickness, solubility of drug in tablet core, level of leachable pore-forming agent(s) and the osmotic pressure difference across the membrane[26-27]

There are several obvious advantages inherent to the CPOP system. The stomach irritation problems are considerably reduced, as drug is released from the whole of the device surface rather from a single hole.[27]

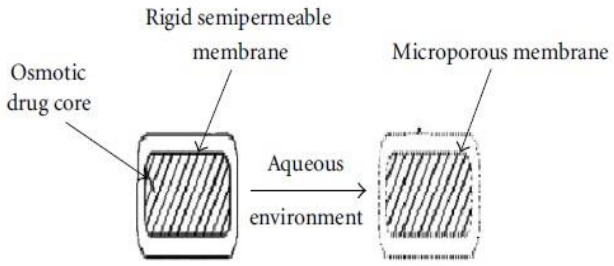

Figure 9: controlled porosity osmotic pump

BASIC COMPONENTS OF OSMOTIC SYSTEMS

Drug;

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

Semi-permeable membrane;

An important part of the osmotic drug delivery system is the semi-permeable 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.[28] 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.[29]

Flux regulators;

Delivery systems can be designed to regulate the permeability of the fluid by incorporating fluxregulating 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.[30]

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 alcohol, butyl alcohol, 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.[31]

Wicking agent;

A wicking agent is of either swellable or non-swellable nature. They are characterized by having the ability to undergo physiosorption with water. Physiosorption is a form of absorption in which the solvent molecules can loosely adhere to surface of the wicking agent via Van der waals interactions between the surface of the wicking agent and the absorbed molecule. The function of the wicking agent is to carry water to surfaces inside the core of the tablet there by 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 in weight poly (vinyl pyrolidone) PVP , m-pyrol, bentonite, magnesium aluminium silicate, polyester and polyethylene. SLS, colloidal silica and PVP are non swellable wicking agents.[32]

Pore forming agent;

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. Thepore-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.[33]

Plasticizers;[34]

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

behaviour 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
Diacetate- for low permeability
Tri ethyl citrate
Diethyl tartarate or Diacetin- for more permeable films

Osmotic agent;[35-37]

These are also known as 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.

Some of the commercially used osmotic agents;

Sodium chloride, Fructose, Sucrose, Potassium chloride, Xylitol, Sorbitol, Citric acid, Dextrose,

Manitole and Lactose.

Some Mixture Used As an Osmotic Agent;

- Dextrose +Fructose
- Lactose +Fructose
- Sucrose+ Fructose
- Lactose +Dextrose
- Mannitol +Fructose
- Mannitol +Dextrose
- Dextrose +Sucrose
- Mannitol +Sucrose

APPLICATION:[38]

Osmotically controlled oral drug delivery system utilize osmotic pressure for controlled delivery of active agent.

Alza corporation of USA was first to develop an oral osmotic pump,even today they are leaders in this field with a technology named OROSTM.

Osmotic pumps have made tremendous progress and the available products based on this technology and number of patents granted in the last few years makes its presence felt in the market.

Apart from drug delivery osmotic pumps can be used as experimental tools to determine important pharmacokinetic parameters of new existing drugs.

Elementary osmotic pumps are suitable for delivery of drugs having moderate water solubility.

Push-pull osmotic pumps can be used for delivery of drugs having extremes of water solubility

ADVANTAGES[39-43]

- 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.
- In the osmotic pump tablet frequency of dosing is reduced due to drug being released over a longer period of time unlike conventional tablets
- The delivery rate of zero-order is achievable with osmotic systems.
- Delivery may be delayed or pulsed, if desired.
- Higher release rates are possible with osmotic systems compared with conventional diffusion-controlled drug delivery systems.
- For oral osmotic systems, drug release is independent of gastric pH and hydrodynamic conditions.
- The release from osmotic systems is minimally affected by the presence of food in gastrointestinal tract.
- A high degree of in vivo- in vitro correlation (IVIVC) is obtained in osmotic systems.

DISADVANTAGES;

Release rate: The drug release rate can be altered by food and gastric transit time; as a result differences may arise in the release rate between doses.

Can not crush or chew products: Osmotic pump tablet should not be crushed or chewed as it can lead to loss of the 'slow release' characteristics as well as toxicity.[44]

MARKETED PRODUCT[45]

Elementary Osmotic Pump

Brand Name	API
Efidac 24	Chlorpheniramine
Acutrim	Phenylpropanolamine
Sudafed 24	Pseudoephedrine
Volmax	Albuterol
Minipress XL	Prazocine

Push-Pull Osmotic Systems

Ditropan XL	Oxybutynin chloride
Procardia XL	Nifedipine
Glucotrol	Glipizide
Covera HS	Verapamil HCl
DynaCirc CR	Isradipine
Invega	Paliperidone

Implantable Osmotic Systems

Viadur	Leuprolide acetate
Chronogesic	Sufentanil

CONCLUSION;

Osmotic drug delivery system are known to provide prolonged and controlled release of the drugs their by maintaining the effective concentration at the target site for longer duration.The osmotic delivery of drugs based on above review of the system.osmotic drugs delivery system is observed to provide a better delivery system of drugs intended for better therapeutic efficacy.

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Conflicts of Interest: The authors declare no conflicts of interest.

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