SINGLE LAYER OSMOTIC CONTROLLED RELEASE TABLET - A COMPREHENSIVE REVIEW

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Abstract:

This review article focuses on the Novel drug delivery system by using the Elementory osmotic pump tablet by using different types of components such as drug, osmotic agent, wicking agent, pore forming agent delivery orifice, etc. We have also studied in this review article about the Osmotic drug delivery system, its classification, its various advantages and disadvantages, principle of osmosis, classification of osmotic drug delivery system. We had also studied about the different various factors for the evaluation of elementary osmotic pump tablet.

Keywords: Osmosis, Osmotic Drug Delivery System, , NDDS, Elementary osmotic drug tablet, etc.

Introduction

Oral, controlled-release (CR) systems for extended release of active pharmaceutical ingredients (API's) have provided advantages of safety (improved Cmax/Cmin ratio) and convenience (reduced daily dosings) over immediate release (IR) dosage forms for numerous API's. CR dosage forms most often have employed matrix or osmotic technologies. Matrix technology [1] sustains the release of an API in the gastrointestinal tract (GIT) by a combination of API diffusion and matrix erosion. Osmotic API delivery technology involves the use of osmotic pressure exerted on a core surrounded by a semi-permeable membrane to pump API out at a steady rate [2–6]. While matrix technology is generally regarded as simpler to manufacture, osmotic technology is less dependent on API properties (solubility, pH and fed state sensitivity) and especially useful for low solubility API's. In an elementary osmotic system, the device is in the form of a tablet consisting of a solid core surrounded by a water-permeable, water insoluble membrane. Aqueous body fluids enter the system continuously through the membrane and dissolve the solid API contained within the core. The API is then released through an orifice in the membrane once sufficient pressure is built

up to cause the solution containing the API to be pushed through the orifice. When the API present in the core is able to produce a sufficiently high osmotic pressure of its own or when additives are present to increase the osmotic pressure (i.e., osmagents), the API is released at a predetermined rate. The prerequisite for achieving this effect is a sufficiently high solubility of water-soluble API such that the amount of water entering the core through the water-permeable membrane is sufficient to dissolve most of the API in the core. As a result, the API is delivered from the tablet predominantly in solution. When the solubility is insufficient, solubilizing additives can sometimes still enable the use of elementary osmotic tablets. For API's that have low-solubility in the GIT, osmotically controlled delivery of the API is more difficult, with elementary osmotic systems generally being considered unsuitable. One approach for solving this problem involves a two-part system, also known as a “push–pull” system [7,8]. In a push–pull system, the API or API formulation is present in one layer and water-swellable polymers or hydrogels with an osmagent are present in a second layer of a tablet. The tablet core is coated with a semipermeable membrane which has a hole placed through it on the API side of the coated tablet. Fluids entering the system cause an increase in volume of the swellable part, which in turn acts to help expel the contents of the API from the system. Compared with conventional immediate release tablets, the preparation of these tablets is complicated. Not only does this system require a more complex bilayer press to prepare tablet cores, but also, stringent demands are placed on the properties of the two formulations being compressed together to form a cohesive core. In addition, during the manufacturing process, the coated tablets must be oriented so that the delivery orifice is made only on the side containing the API. Because of the need for two layers, this system has generally been limited to doses of active API or combination of API and functional additives lower than about 200 mg. Examples published in the literature suggest that single-layer osmotic API delivery of low solubility API's is possible [9–12], but do not define the limitations or optimal formulation factors for such systems. In the current investigation, factors that influence the successful delivery of low solubility API's from a single-layer osmotic system are reported. From these studies, a general platform technology is described which functions effectively for a wide range of API's.

Historical Aspects of Osmotic Pumps

About 75 years after discovery of the osmosis principle, it was first used in the design of drug delivery systems [13]. 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.

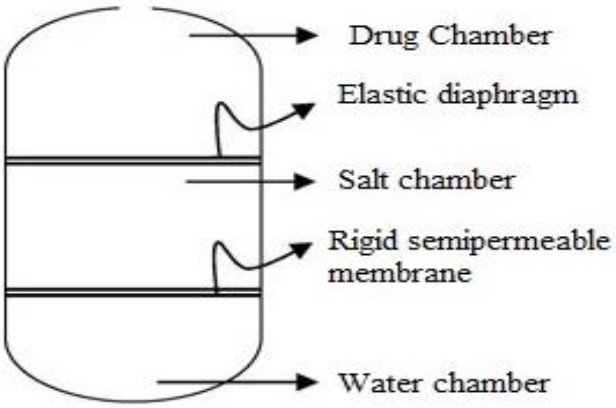

Figure 1: Rose-Nelson Pump

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 thedevice 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 drug [14]. 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 [15].

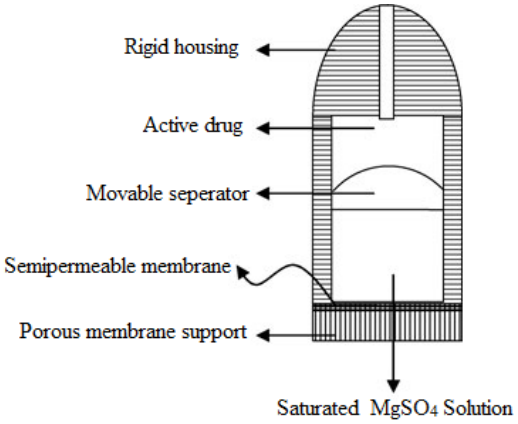

Figure 2: Higuchi-Leeper Pump

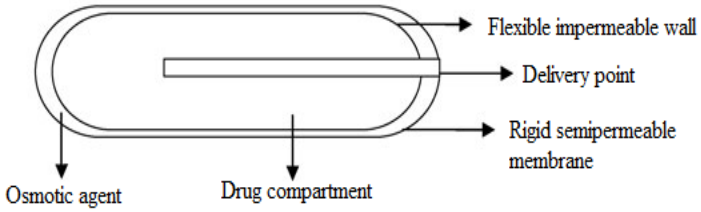

Figure 3: Theeuwes miniature osmotic pump

In 1975, the major leap in osmotic delivery occurred as the elementary osmotic pump for oral delivery of drugs was introduced. The pump consists of an osmotic core containing the drug, surrounded by a semi permeable membrane with a delivery orifice. When this pump is exposed to water, the core imbibes water osmotically at a controlled rate, determined by the membrane permeability to water and by the osmotic pressure of the core formulation. As the membrane is nonexpandable, the increase in volume caused by the imbibitions of water leads to the development of hydrostatic pressure inside the tablet. This pressure is relieved by the flow of saturated solution out of the device through the delivery orifice. This process continues at a constant rate until the entire solid agent inside the tablet has been dissolved and only a solution filled coating membrane is left. This residual dissolved agent continues to be delivered at a declining rate until the osmotic pressure inside and outside the tablet is equal. Normally, the EOP delivers 60-80% of its contents at a constant rate, and there is a short lag time of 30-60 min as the system hydrates before zero order delivery from the EOP is obtained [16].

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).

Principles of Osmosis- [17, 18]

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.

Osmotically controlled drug delivery systems- [19]

Osmotic pressure is used as driving force for these systems to release the drug in controlled manner. Osmotic drug delivery technique is the most interesting and widely acceptable among all other technologies used for the same. Intensive research has been carried out on osmotic systems and several patents are also published. Development of osmotic drug delivery systems was pioneered by Alza and it holds major number of the patents analyzed and also markets several products based on osmotic principle. These systems can be used for both route of administration i.e. oral and parenterals. Oral osmotic systems are known as gastro-intestinal therapeutic systems (GITS). Parenteral osmotic drug delivery includes implantable pumps.

a. **Type I:** Single compartment. In this design, the drug and the osmotic agent are located in the same compartment and are surrounded by the semi permeable membrane (SPM). Both the core components are dissolved by water, which enters the core via osmosis. A limitation is the dilution of drug solution with the osmotic solution, which affects the release rate of the drug from the system. Additionally,

water incompatible or water-insoluble drugs cannot be delivered effectivelyfrom a single compartment configuration.

b. **Type II:** Multiple compartments. In this design, drug is separated from the osmotic compartment by an optional flexible film, which is displaced by the increased pressure in the surrounding osmotic compartment, which, in turn, displaces the drug solution or suspension.

The type II system inherently has greater utility than type I systems and can deliver drugs at a desired rate independent of their solubilities in water. One main advantage of these systems is their ability to deliver drugs that are incompatible with commonly used electrolytes or osmotic agents.

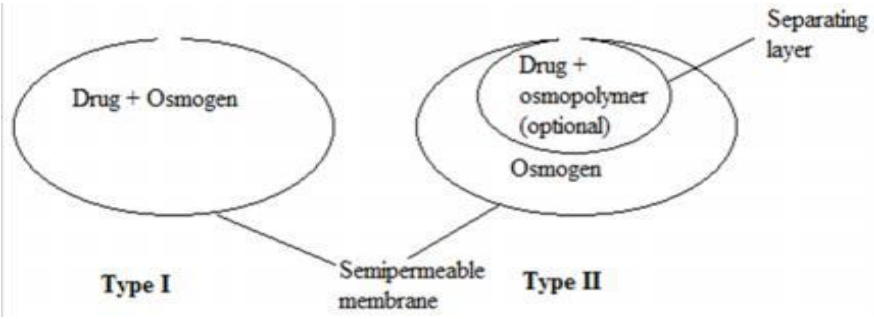

Figure 4: Classification of osmotic delivery systems: types I and II.

Advantages [20, 21]:

Osmotic drug delivery system for oral and parenteral use offer distinct and practical advantage over other means of delivery. The following advantages contributed to the popularity of osmotic drug delivery systems.12

- 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.
- 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 osmotic ally base technologies.

- 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.

Disadvantages [22, 23]:

- 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.

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 [24]. 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 [25].

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 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 [26].

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 hyric 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 [27].

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 [28]. 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

Elementary osmotic pump (EOP) [29, 30]:
The was introduced in 1970s to deliver drug at zero order rates for prolonged periods, and is minimally affected by environmental factors such as pH or motility. The tablet consists of an osmotic core containing the drug surrounded by a semipermeable membrane laser drilled with delivery orifice. Following ingestion, water in absorbed into system dissolving the drug, and the resulting drug solution is delivered at the same rate as the water entering the tablet. The disadvantages of the elementary pump are that it is only suitable for the delivery of water soluble drugs.

Factors affecting the release rate from Elementary Osmotic Pump System:
There are following factors which should be considered while designing an EOP. These factors are also applicable to other osmotic drug delivery systems:

- Membrane thickness.
- Osmotic pressure.
- Type of membrane and characteristics.
- Solubility.
- Seize of the delivery orifice.
- Use of Wicking agent.
- Type and amount of plasticizer.

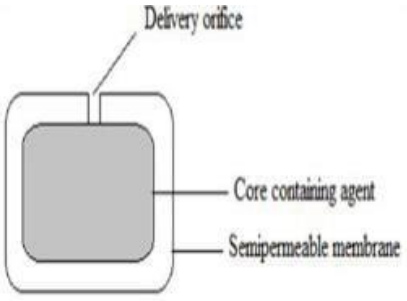

Figure 5: Elementary osmotic pump

Conclusion:

When we talk about the novel drug delivery system, the osmotic drug delivery system is an effective approach in this sector. Generally, the different types of osmotic drug delivery system were used for better bioavailability. There are various evaluation parameters are used to evaluate the elementary osmotic pump tablet such as friability, drug uniformity, orifice size, orifice pressure, etc. We can conclude from this review article that the elementary osmotic pump tablets are very important drug delivery tool which is used for incorporation or targeting of drug for various therapeutic activities and provides various advantages over other drug delivery tools. The Elementary osmotic drug delivery tablet will be proved as a great reward for the future perspective.

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