A REVIEW ON ELEMENTARY OSMOTIC PUMP TABLET AND ITS EVALUATION FACTORS

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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-
Novel drug delivery systems (NDDS) are the main area of pharmaceutical research and Expansion. The aim is moderately little expansion charge and period mandatory for presenting a NDDS as related to novel chemical entity. Numerous conventional drug delivery systems have been planned to modify the release a medicine over an prolonged period of a time [1]. Numerous proposals are accessible to control or modulate the drug release from a dosage formulae. Majority of oral CR dosage forms fall in the group of matrix, reservoir or osmotic systems. Conventional matrix or reservoir kind preparations exhibits difficulty of bioavailability variations due to gastric pH differences. Additionally, the release of medications from these systems is affected by the hydrodynamic circumstances of the body. The rate and extent of drug absorption from conventional formulations may differ significantly depending on the factors such as physico-chemical belongings of the medication, existence of Excipients, physiological factors such as existence or nonappearance of food, pH of the gastro-intestinal tract (GI) and so on [2]. However, drug release from oral measured release dosage forms may be affected by pH, GI motility and existence of food in the GI tract [3].

Unoriginal oral medication quantity forms are recognized to deliver a prompt release of energetic ingredients, but one cannot regulate the release of the medication and cannot conserve a healing concentration at the preferred site for a long time [4]. Numerous features affect the rate and extent to which the drug influences complete circulation after administration, including the excipients used, physicochemical belongings of the active component, physiology and pH of the stomach tract, gastric emptying rate, and GI motility [5,6]. As the drug concentration in plasma differs with a conventional amount form, it is challenging to obtain a steady-state drug concentration in plasma. These fluctuating medicine stages may hamper the attaining and preserving of an effective application, which may result in an unwanted medicine response or may not yield a healing response [7]. To overcome these boundaries with conventional quantity forms, controlled-release drug delivery systems, through which the medicine is released in a expected and sustained method, have been developed. They preserve the drug application between the lowest effective concentration (MEC) and maximum therapeutic concentration (MTC) for a extended time, confirming sustained healing action [8,9, 10]. Amongst the several controlled-release systems, osmotic drug delivery systems provide substantial advantages. Since these systems preserve uniform plasma medication concentrations and deliver a sustained therapeutic response, they decrease the dosing frequency and subsequently improve patient compliance [11]. Moreover, they release medications at a rate that is independent of physiological factors, including GI motility, nutrition, pH, and the hydrodynamics of the dissolution medium. This effects in comparable release designs and an outstanding in vitro/in vivo correlation. Additional greater benefit of osmotic systems is that they are appropriate for use with medications that have a wide range of water solubility and are easy and simple to formulate, drive, and scale up [12]. Osmosis can be defined as the net movement of water through a selectively permeable film due to burden [13]. There is a concentration variance of the solute across the film, which is semi-permeable, generating pressure. Water is permitted to pass through this film, and solute particles are frequently not allowable to as this film is selectively penetrable. The pressure applied to the higher-solute-concentration side to resist solvent flow is called the osmotic pressure [14]. Osmosis can also be defined as the movement of water from a area with a higher concentration to a area with a lower concentration across a semi-permeable film [15]. Osmotic delivery systems or osmotic pumps are chiefly composed of a principal containing a medicine and an osmogen. These are coated with a semi-permeable film containing one or more ports for drug delivery, such that the drug is released over time in the method of a solution or suspension [16]. Oral osmotic systems are composed of a compressed tablet core covered with a semi-permeable membrane through which distribution orifices are shaped using a laser beam or mechanical drill [17]. These measured systems are based on osmosis and osmotic pressure and are independent of several gastrointestinal reasons. However, it is noteworthy that there are serious issues that effect the plan of osmotically controlled drug delivery systems, including the drug solubility, delivery orifices, osmotic pressure, semi-permeable film, type and nature of the polymer, membrane thickness, and kind and quantity of plasticizer [18, 19].

Advantages of Osmotic Drug Delivery System [20,21]-

Separately from the general benefits of controlled drug delivery systems, osmotic pumps have Certain irreplaceable advantages, as follows:

- Delivery of medication from osmotic pumps can be planned to follow true zero-order kinetics.
- Delivery may be delayed or pulsed, if desired.
- Medicine release from osmotic pumps is independent of the gastric pH and hydrodynamic situations of the body.
- Higher release rates are possible from osmotic systems than with conventional diffusion Based drug delivery systems.
- The delivery rate of drug(s) from these systems is highly expectable and programmable by controlling the release control restrictions.
- A high degree of *In vitro/In vivo* association can be gained from osmotic pumps.
- Drug release from the osmotic systems is slightly affected by the occurrence of food.

Disadvantages of Osmotic Drug Delivery System-

- Improvement expenditures: Costly particular equipment and inert constituents may be necessary for osmotic pump tablet preparations.
- Release rate: The medicine release rate can be transformed by food and gastric transit time; as a result variances may arise in the release rate between doses.
- Cannot crush or grind products: Osmotic pump tablet should not be crushed or chewed as it can lead to loss of the 'slow release' features as well as toxicity [22].

Osmosis-

Process of movement of the solvent from the lower concentration of solution to the higher concentration of the solution through the semipermiable membrane. Osmosis is the process that can control the drug delivery system. Osmotic pressure shaped due to imbibitions of fluid from external atmosphere into the dosage form regulates the delivery of medicine 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 belongings of a solution in which the magnitude of osmotic pressure of the solution is independent on the number of separate entities of solute present in the solution. Hence the release rate of medicines from osmotic dispensing devices is dependent on the solubility and molecular mass and activity coefficient of the solute (osmogent) [23].

Principle of Osmosis -

The first report of an osmotic outcome dates to Abbenollet (1748). But Pfeffer gained the first quantitative capacity in 1877. In Pfeffer investigation a film penetrable 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

$\pi = \Phi c r t$

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 generally used in controlled release preparation are tremendously high ranging from 30 atm for sodium phosphate up to 500 atm for a lactose-fructose mixture, as their osmotic pressure can yield high water flow across semi permeable film. The osmotic water flow through a membrane is given by the equation

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

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

$\Delta \pi$ is the osmotic pressure difference between the two solutions on either side of the film. This equation is harshly for entirely perm selective membrane that is membrane penetrable to water but completely impermeable to osmotic agent [24]

List of Some Important Patents Based on Osmotic Drug Delivery [25]-

System type	Drug	U S Patent	Year
Elementary osmotic pump	Indomethacin	4265874	1981
Elementary osmotic pump	Haloperidol	4610686	1986
Elementary osmotic pump	Chlorpheniramine	4857330	1989
Elementary osmotic pump	Nicotine	5147654	1992
Elementary osmotic pump	Nystatin	5776493	1998
Elementary osmotic pump	Levodopa	5869096	1999
Second expandable osmotic chamber	Procainamide HCl	4331728	1982
Second expandable osmotic chamber	Verapamil	5156850	1992
Second expandable osmotic chamber	Zafirlucast	6224907	2001
Multichamber osmotic system	Diltiazem	4859470	1989
Multichamber osmotic system	Tandospirone	5185158	1993
Multichamber osmotic system	Glipizide	5545413	1996
Multichamber osmotic system	Captopril	5976571	1999
Multichamber osmotic system	Captopril	6207191	2001
Multichamber osmotic system	Nifedipine	6352721	2002

Basic Components of Osmotic Pump Systems [26, 27]-

- **Drug-**

  Not each administered medicine wants to deliver a extended response, so the osmotic pump system is not appropriate for all medicines. Medicines that are directed for the extended action of sicknesses with a biological half-life in the range of 1–6 h are best suited for osmotic systems. Drugs with a biological half-life shorter than 1 h are not good candidates, and, equally, medicines with a half-life greater than 12 h are also not good candidates for controlled release in an osmotic pump system. The drug's half-life should be little so that it can be sustained or maintained in plasma, and its extended release should be the necessity [28]. To be combined into this system, drugs should also be neither highly soluble nor very poorly soluble, and the environment of the drug should be potent for this purpose [29, 40].

- **Osmotic Agent-**

  Osmogens and osmogents are other names for osmotic mediators, and they produce the osmotic pressure in the osmotic delivery system. When a drug has little solubility, it will be out at an unhurried, first-order rate; to create this release rate more rapidly, osmotic mediators are used in the preparation. These mediators make a high gradient of osmotic pressure within the osmotic system; thus, the rate of drug release rises [41]. The osmotic mediators existing on the market include lactose, fructose, sorbitol, dextrose, sodium chloride, citric acid, potassium chloride, sucrose, xylitol, and mannitol. Osmogens may also contain of mixtures, such as mannitol + sucrose, dextrose + fructose, sucrose + fructose, dextrose + sucrose, mannitol + fructose, lactose + fructose, mannitol + dextrose, or lactose + dextrose [42]. Drugs with worthy water solubility can be used as osmotic mediators, such as mannitol, glycerol, lactulose, sorbitol, or polyethylene glycol. However, osmogenic salts (e.g., sodium chloride and potassium chloride) and sugars can be merged into the preparation if the drug itself does not possess osmogenic activity. Hence, water solubility and osmotic activity are the two most important cause factors when choosing osmotic mediators [43].

- **Semipermeable Membrane-**

  As the environment of the osmotic system membrane is selectively permeable, the polymer should be selectively permeable, to allow for the route of water only, and should be impermeable to solutes [44]. In osmotic pump preparation, the polymer that is most generally and extensively used is cellulose acetate, which is provided in several marks of acetyl content [45]. The marks holding 32% and 38% acetyl content are most generally working. The degree of replacement (average no. of hydroxyl groups replaced by substituting groups) regulates the acetyl content. Other digestive polymers used for this determination contain cellulose esters, like diacetate, propionate, cellulose acetate, triacetate, and cellulose acetate butyrate. Ethers of cellulose can also be involved in this, such as ethyl cellulose [46,47]. The material must have adequate wet strength to retain the integrity of its dimensions, which is advantageous for the device. The capability of the material to allow water permeation must be adequate so that the flux rate of water breaks within the required range. The transmission rates of water vapour can be designed to assessment the water change rates. The biocompatibility of the membrane material should also be considered [48].

Common biocompatible polymers contain PEG, HPMA, PGA, chitosan, and dextran. These materials, when used in oral systems, can be consumed and then expelled in feaces, once the osmotic pump is exhausted. Oral and implant fractions that may have been absorbed are very likely to be eliminated by glomerular filtration in the kidney, provided that they are below the glomerular threshold [49].

- **Wicking Agent [37]-**
  Wicking agents are components with the ability to absorb water into the porous network of a delivery system. Their main function is to carry solvent molecules to surfaces inside the core of the osmotic device, thereby creating channels of heightened surface area. A wicking agent is selected based on its nature, either swellable or non-swellable, and based on its ability to undergo physical adsorption with solvent molecules. Physical adsorption is a form of vander Waals interaction where the solvent molecules can loosely adhere to the surface of the wicking agent [50]. Sodium lauryl sulfate, polyvinylpyrrolidone, and colloidal silicon dioxide are examples of such agents [51].

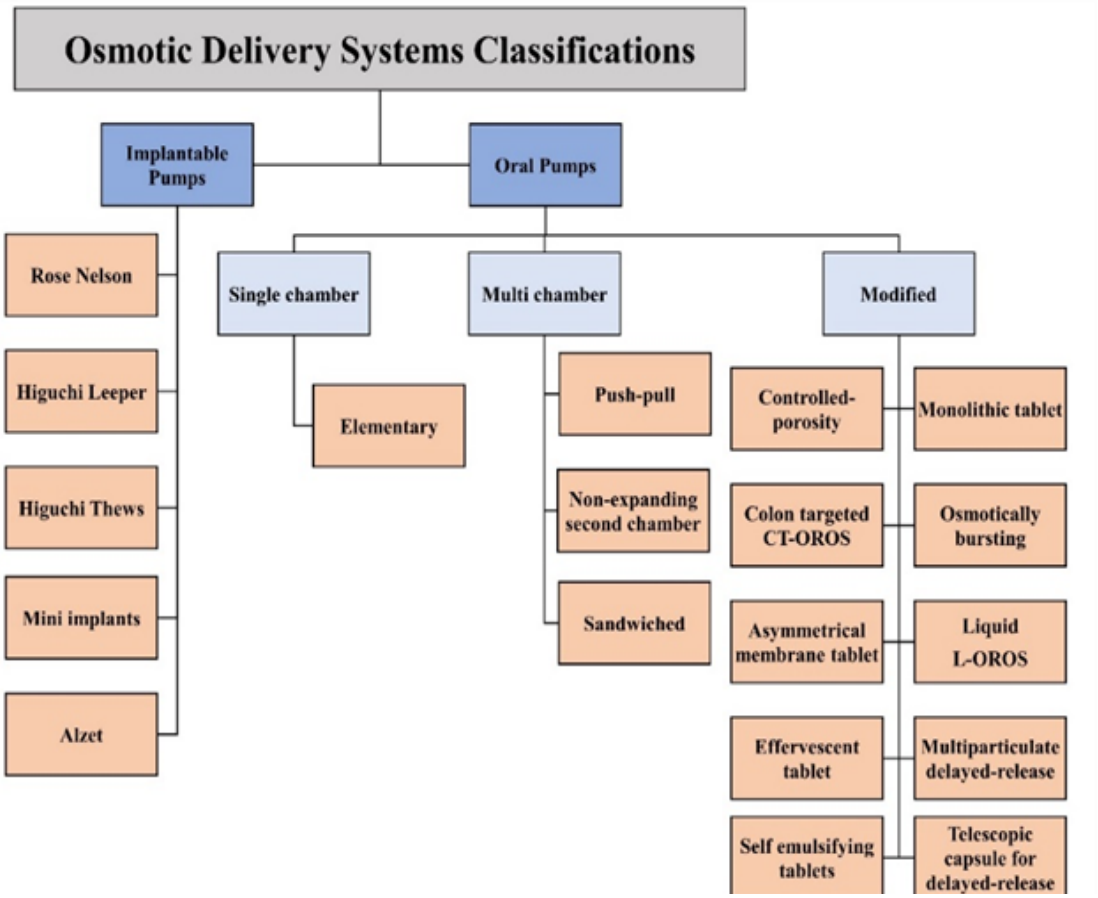
- **Pore-Forming Agents-**
  A microporous membrane forms due to the existence of pore-forming mediators. A pore former can also form walls with micro-sized pores. This pore former leaches out, creating pores as the system operates [52]. Alkaline metal salts such as potassium chloride, sodium chloride, and others may be used as pore-forming agents. Alkaline earth metals such as calcium nitrate and carbohydrates such as fructose and glucose can also be working for this determination [53].

- **Coating Solvents-**
  The solvent system delivers the polymer, which is dispersed or dissolved, and other additives to the substrate surface as its primary function. Solvents that are inert and either organic or inorganic in nature are employed to prepare a polymeric solution [54]. These solvents should not cause adverse actions in the core or other materials. Examples of such solvents include methanol, cyclohexane, methylene chloride, isopropyl alcohol, and water [55].

- **Delivery Orifice-**
  The medication is distributed done an orifice via the procedure of dispersion to attain an optimal, zero-order drug [56- 59]. The cross-sectional area of the orifice must be minor, but it must not be too small in mandate to generate hydrostatic pressure in the osmotic system. This means that the orifice must be greater than the smallest size necessity. The delivery orifice can be formed via a simple mechanical piercing method [60]. Extra technique used to generate orifices in the sub-millimeter series is laser drilling skill. The laser beam usually used for this resolution is CO2, and it has evidenced to be helpful and inexpensive [61,62]. Leaching resources can also be engaged for making in situ orifices or pores in the film [63]. There is a method well-known as indentation in core tablets that develops modernized compression punches. The upper punch comprises needles for the formation of orifices [64].

Types of Osmotic Drug Delivery Systems [65]-

Depending on the active element, plan, and resolution of habit, osmotic systems are principally classified as shown below-



Elementary Osmotic Pump (EOP)-

An EOP is a novel arrangement for medication distribution through an osmotic system developed by Theuwes in 1974. The discharge rate can be controlled by controlling the penetration capability of the semi-permeable film and the preparation characteristics [66]. In the creation of this method, the medication is compacted into a tablet, and then a coating of a semi-permeable cellulose acetate film is shaped around it [67]. An orifice of about 0.5 to 1.5 mm is drilled in this film. A mechanical drill can be used for this determination, but it can also be carried out by laser drilling using a CO2 laser beam with a 10.6-micron wavelength. Once the method is put into process, water arrives through a semi-permeable wall by imbibition into the core, generating osmotic pressure. The medication explanation volume is proportional to the solvent capacity [68]. The rate of medication release is zero-order, which means that it is constant. The development of zero-order rates from the system wants a half-hour to one-hour lag stage before continuous delivery begins. About 60–80% of the medication has a constant medication release rate. Drugs with moderate water solubility are measured appropriate for this system [69].

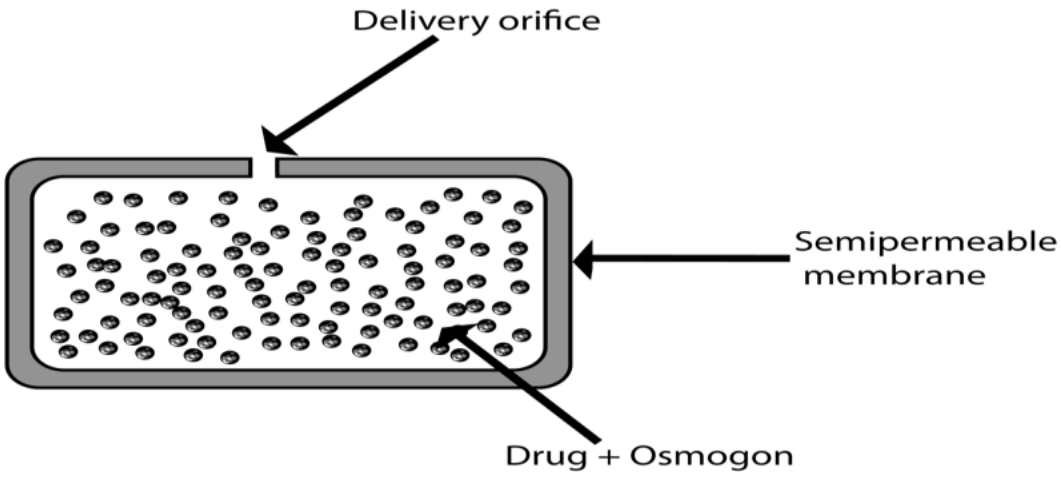


Fig- The structure of an EOP

Factors Affecting The Design Of Osmotic Controlled Drug Delivery Systems-

- **Solubility -**
  The distribution rate of a medicine from an osmotic pump depends to a great range on the solubility of medication at saturation. Candidate medications for osmotic distribution have water solubility in the diverse variety. However, by modulating the solubility of these medications inside the core, actual discharge arrangements may be gained for the medications, which might otherwise seem to be poor applicants for an OCODDS. Some of examples are co-compression of the medication with excipients, which modulate the solubility of the medication within the core [70].
- **Thickness-**
  Width of the core tablets and coated tablets were measured by using screw gauge. Ten tablets from each preparation were randomly particular and used. Thickness is conveyed in millimeters.
- **Hardness**
  The hardness of the core tablets and coated tablets were measured using the Pfizer hardness tester. Six tablets from every preparation were unsystematically particular and used. The regular hardness and the ordinary deviation were calculated. It is expressed in Kg/cm2.
- **Friability-**
  Friability of the matrix tablets and core tablets of permeable osmotic pump tablets were determined. 10 tablets were unsystematically particular, weighed and located in the Roche Friabilator. The apparatus was swapped at 25 rpm for 4 min. After revolutions the tablets were dedusted and weighed again. The percentage friability was measured using the formula,

  $$\% \text{ Friability} = \frac{\text{Initial wt. of tablets} - \text{Final wt. of tablets}}{\text{Initial wt. of tablets}} \times 100$$

- **Weight uniformity-**
  Ten tablets were unsystematically particular from every batch and separately weighed. The average weight and standard deviation of 20 tablets was calculated [71].

- **Size of delivery orifice-**
  Some of the techniques to produce a distribution orifice in the osmotic tablet coating are use of a mechanical dril, laser drilling, use of an device with slidable punches, indentation that is not covered during the coating procedure, and use of leachable ingredients in the coating. The size of the distribution orifice must be slighter than the maximum size Amax to reduce the solute diffusion through the orifice. Also, it must be adequately great, above a smallest size a min, to reduce hydrostatic pressure inside the arrangement that would affect the zero-order release rate. Great hydrostatic pressure can also lead to the distortion of the device, thereby resulting in unpredictable drug distribution.
- **Orifice size-**
  The orifice must be lesser than a extreme size to reduce drug distribution by diffusion through the orifice. Furthermore, the area must be adequately large, above a smallest size to lessen hydrostatic pressure buildup in the arrangement. Therefore, the cross-sectional area of the orifice should be continued between the smallest and extreme standards. This technology is well recognised for creating sub- millimeter size hole in tablets. Use of leachable materials in the semipermeable coating: e.g. controlled porosity osmotic pump.
- **Osmotic pressure-**
  The osmotic pressure π directly affects the release rate. To achieve a zero-order release rate, it is crucial to keep π constant by continuing a saturated solute solution. In this case, other osmotic agents are added that improve osmotic pressure. For example, addition of bicarbonate salt not only delivers the essential osmotic gradient but also stops blockage of the orifice by triggered drug through creating an effervescent action in acidic media.
- **Semipermeable membrane-**
  Since the semipermeable film is porous to water and not to ions, the release rate is fundamentally independent of the pH of the environment. Additionally, the medication dissolution procedure takes place inside the distribution system, completely disconnected from the environment [72].
- **Osmotic agents-**
  Osmotic agents continue a concentration gradient across the film. They also produce a driving force for the acceptance of water and assist in continuing medication equality in the hydrated planning. Osmotic ingredients frequently are ionic groupings comprising of any 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.
- **Flux regulators-**
  Delivery systems can be intended to control the penetrability of the watery by integrating flux regulating agents in the sheet. Hydrophilic materials such as poly ethylene glycols (300 to 6000 Da), polyhydric alcohols, poly alkylene glycols, and the like progress the flux [73].

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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