Review Article

A Review on Osmotic Drug Delivery System

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ABSTRACT

Novel drug delivery system is the key of pharmaceutical research & development. Many conventional drug delivery systems have been designed to modulate or modified the release a drug over an extended period of a time. Osmotic drug delivery system (ODDS) used the basic principle of osmotic pressure for controlled release of drugs. Because of that to maintain drug concentration within therapeutic window & minimize side effect. This review highlights the theoretical concept of drug delivery, principle, and types of osmotic drug delivery system, general consideration, and advantage, disadvantages of this system.

Keywords: Novel drug delivery system, osmosis, osmotic drug delivery system, osmotic pressure, controlled formulation, osmotic pump.

INTRODUCTION

In recent year, considerable attention has been focused on the development of novel drug delivery system (NDDS) osmotically controlled drug delivery system (ODDS) are the type of NDDS which utilize osmotic pressure for controlled delivery of active agent. The release of drug from osmotic system is independent of gastric pH &gastric motility. However, drug release from oral controlled release dosage forms may be affected by pH, GI motility and presence of food in the GI tract3. Osmotically controlled drug delivery systems (OCDDS) is one of the most promising drug delivery technology that use osmotic pressure as a driving force for controlled delivery of active agents. Drug release from OCDDS is independent of pH and hydrodynamic conditions of the body because of the semi permeable nature of the rate-controlling membrane and the design of deliver orifice used in osmotic systems, so a high degree of *In vitro/In vivo* correlation is achieved. Osmosis refers to process of movement of solvent from lower concentration of solute towards higher concentration of solute across a semipermeable membrane. Osmotic pressure is minimum pressure which needs to be applied to a solution to prevent the inward flow of its pure solvent across a semipermeable membrane. Osmotic Pump Controlled Release Preparation is a novel drug delivery system with internally drug delivery rate as characteristic and controlled with the osmotic pressure difference between inside and outside of the semipermeable membrane as drug delivery power.

Now days, osmotic tablets have been developed in which the delivery orifice is formed by the incorporation of a leachable component in the coating. Once the tablet comes in contact with the aqueous environment, the water-soluble component dissolves, and an osmotic pumping system result. Subsequently, water diffuses into the core through the micro porous membrane, setting up an osmotic gradient and thereby controlling the release of drug. 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 semipermeable membrane, which is permeable only to the solvent but impermeable to the solute. The pressure applied to the higher-concentration side to inhibit solvent flow is called the osmotic pressure. Recently, osmotic tablets have been developed in which the delivery orifice is formed by the incorporation of a leachable component in the coating. When the tablet interacts with the fluid condition, the water-solvent part breaks up, and an osmotic siphoning framework result. Subsequently, water diffuses into the core through the micro porous membrane, setting up an osmotic gradient and thereby controlling the release of drug. 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 semipermeable membrane, which is permeable only to the solvent but impermeable to the solute. The pressure applied to the higher-concentration side to inhibit solvent flow is called the osmotic pressure.[1-3]

Advantages

- Drug release from osmotic pumps is independent of the gastric pH and hydrodynamic Condition of the body.
- Higher release rates are possible from osmotic systems than with conventional diffusion based drug delivery systems.

- Easy formulation and simple operation.
- The delivery rate of drug(s) from these systems is highly predictable and programmable by modulating the release control parameters.
- Improved patient compliance with reduced dosing frequency.
- It is possible to attain better release rates than those obtained with conventional diffusion
- Drug release from the OCODDSs exhibits significant *in vitro-in vivo* correlation [*IVIVC*] within specific limits.
- Increased safety margin of high potency drugs
- Reduced side effects.
- Drug release from the osmotic systems is minimally affected by the presence of food.
- Delivery may be delayed or pulsed, if desired.
- They are suitable for a wide range of drug.
- Sustained and consistent blood levels within the therapeutic window.
- They are well characterized and understood.
- Reduced interpatient variability. [3,4]

Disadvantage:

- High cost.
- If the coating process is not well controlled there is a risk of film defects, which results in dose dumping.
- Hole Size is critical in case of elementary osmotic system.
- Drug release from the osmotic systems is affected to some extent by the presence of food.
- Retrieval of therapy is not possible in the case of unexpected adverse event
- Rapid development of tolerance
- Integrity and consistency of the coating process is not well controlled there is dose dumpling. The film beads or particles must be instigated to combine into a film with steady properties.
- Laser drilling is capital intensive.
- Hypersensitivity reaction may occur after implantation.[4,5]

Principle of Osmosis

Abbe nollet first reported osmotic effect in 1748, but Pfeiffer (1877) had been the pioneer of quantitative measurement of osmotic effect. Van't hoff established the ideal gas laws by the expression.

$$\pi=n^2RT$$

Where, n^2 represents the molar concentration of sugar in solution, R depicts the gas constant, and t the absolute temperature.[7]

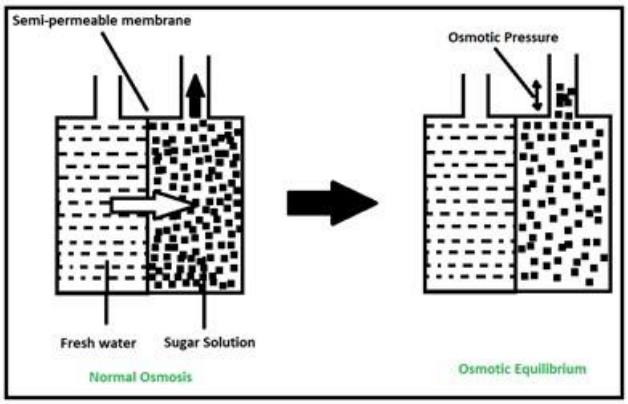

Figure 1: Schematic Illustrating Osmotic Flow and the Attainment of Osmotic Equilibrium

General Considerations and Material Used

Osmotic pump basically contains a medication and semi permeable membrane. In this case, itself may act as an osmogen and shows good water aqueous solubility. On the off chance that the medication doesn't forces any osmogenic salt and other sugar can be joined in the plan. Osmogens are unreservedly water solvent and fit for delivering osmotic weight.

Single osmogen can be used for the formulations and in some case combination of osmogens have been used. Apart from these essential components, other materials such as hydrophilic and hydrophobic polymers and hydrogel. Wicking agent, solubilizing agents surfactants have been utilized depending on the type of formulations. The semipermeable membrane usually contains a plasticizer and in some cases surfactants, flux regulating agent and pore forming agent. Apart from the above materials, common tableting aid such as lubricants, binder, diluents, glidants, wetting agent etc.

Basic Components of Osmotic Pump

1) Osmogens: Drug itself may act as an osmogen and shows great aqueous solubility (e.g. potassium chloride pump). Osmogenes are fundamental ingredient of the osmotic formulation. They include inorganic salts and carbohydrates. Generally, combination of osmogen is utilized to achieve optimum osmotic pressure inside the framework. For the selection of osmogen, the two most critical properties to be considered are osmotic movement and aqueous solubility.

Osmotic agents are classified as:-

i) Inorganic water soluble osmogenes: magnesium sulphate, sodium chloride, sodium sulphate, potassium chloride, sodium bicarbonate.

ii) Organic polymeric osmogens: sodium CMC, HPMC, HEMC

iii) Organic water soluble osmogens: sorbitol, mannitol.

Table 1: List of various osmogens with their osmotic pressure[8]

Osmotic pressures of saturated solution of commonly used osmogens	Osmotic pressure (atm)
Sodium Chloride	356
Fructose	355
Potassium Chloride	245
Sucrose	150
Dextrose	82
Potassium Sulphate	39
Mannitol	38
Sodium Phosphate Dibasic	36
Sodium Phosphate tribasic	31
Sodium phosphate monobasic	28
Lactose-fructose	500
Dextrose-Fructose	450
Sucrose-Fructose	430
Mannitol-Fructose	415
Lactose-Sucrose	250
Lactose-dextrose	225
Mannitol-dextrose	225
Dextrose-Sucrose	190
Mannitol-sucrose	170
Mannitol-lactose	130

2) Wicking agent: It is defined as a material with the ability to water into the porous network of delivery device. The function of wicking agent to or to attract carry water to surfaces inside the of t center he tablet, there by making channels or network of increased surface area .example:- colloidal silicon dioxide, kaolin, titanium dioxide, alumina niacinamide, SLS, low molecular weight poly vinyl pyrrolidone, m-pyrol, bentonite, polyethylene. SLS, Colloidal silica and PVP and non swellable wicking agents.

3) Surfactants: Surfactants are particularly useful when added to wall forming material they produce an integral composite that is useful for making the wall of the device operative the surfactants act by regulating the surface energy of material to improve their blending in to the composite and maintain their integrity in the environment of use during the drug release period. Typical surfactants such as poly oxyethyenated glyceryl recinoleeate, poloxythlenated castor oil having ethylene oxide, glyceryl laureates, glycerol etc.

4) Semi permeable membrane: The semi permeable membrane should be a stable both to the outer and inner environment of the device. The membrane must be adequate unbending in order to hold its dimensional uprightness during the operational lifetime of the device. The membrane must be biocompatible. E.g cellulose acetate, agar acetate, amylosetriacetate, betaglucan acetate, etc.

5) Plasticizers: Plasticizer lower the temperature of the second order phase transition of the elastic modules of the wall and also increase the workability, flexibility and permeability of the fluids generally from0.001 to 50 parts of plasticizer or a mixture of plasticizers are incorporated into 100 parts of wall forming materials. E.g dialkyl phthalates and phthalates, trioctyyl phosphates, benzoates, sulphonamides, glycerolates

6) Pore forming agent: .0These agents are particularly used in the pump development for poorly water soluble drug and in the development of controlled porosity osmotic pump these pore forming agent cause the formulation of microporous membrane these microporouse wall may formed in situ by a pore-former by leaching during the operation of the system. The pores may also be formed in the wall prior to operation of the system. By gas formation within coating polymer solutions which result in void and pore in the final form of wall. The pore formers can be inorganic or organic and solid or liquid in nature. E.g. sodium chloride sodium bromide, potassium chloride, potassium sulphate, potassium phosphate etc.

7) Solubilizing Agents: Non - swellable solubilizing agent are classified into three groups

- Agents that inhibit crystal formation of the drug or otherwise act by complexation of drug (e.g PVP, PEG, cyclodextrins),
- a high HLB micelle forming surfactant, particularly anionic surfactant (e,g Tween 20,60,80,poly oxy ethylene or polyethylene containing surfactants and other long chain anionic surfactants such as SLS)
- Citrate esters and their combination with anionic surfactants (e.g.alkyl esters particularly triethyl citrate)

8) Flux regulators: Flux regulating agents or flux enhancing agent or flux decreasing agent are added to a wall forming material it assists in regulating the fluid permeability through membrane.

Poly hydric alcohols such as poly alkylene glycols and low molecular weight glycols such as poly propylene, poly buylene and poly amylene, etc. can be added as flux reguators.

9) Coating solvents: Solvent suitable for making polymeric solution that is used for manufacturing the wall of the osmotic device include inert inorganic and organic solvents.

Example: methylene chloride, acetone, methanol, ethanol, isopropyl alcohol, ethyl acetate, cyclohexane, etc.

10) Hydrophilic and hydrophobic polymers: Used in the formulation development of osmotic systems containing drug matrix core.

- Selection of polymer is based on:-
  - solubility of drug

- the amount and rate of drug to be released from the pump

Example of hydrophilic polymers

- HEC (hydroxyl ethyl cellulose
- HPMC (hydroxyl propyl methyl cellulose)
- CMC (carboxy methyl cellulose)

Example of hydrophobic polymers

- EC (ethyl cellulose)
- Wax materials etc. [3,4]

CLASSIFICATION OF OSMOTIC PUMP

1. Oral osmotic pump

A. Single chamber osmotic pump

i. Elementary osmotic pump

B. Multi chamber osmotic pump

i. Push pull osmotic pump,

ii. Osmotic pump with non-expanding second chamber

2. Implantable osmotic pump

i. The Rose and Nelson Pump

ii. Higuchi Leeper Pump

iii. Higuchi Theeuwes pump

iv. Implantable Mini osmotic pump

3. Specific types osmotic pump

i. Controlled porosity osmotic pump

ii. Osmotic bursting osmotic pump

iii. Liquid OROS

iv. Delayed delivery osmotic pump

v. OROS CT (colon targeting) osmotic system

vi. Sandwiched oral therapeutic system

vii. Osmotic pump for insoluble drugs

viii. Monolithic osmotic system and OSMA

Xi. Telescopic capsule for delayed release[4, 7]

1. Oral osmotic pump

A. Single chamber osmotic pump

i. Elementary osmotic pump:

Composition: It contains an active agent having a suitable osmotic pressure .it fabricate as a tablet coated with semi permeable membrane usually semi-permeable membrane.

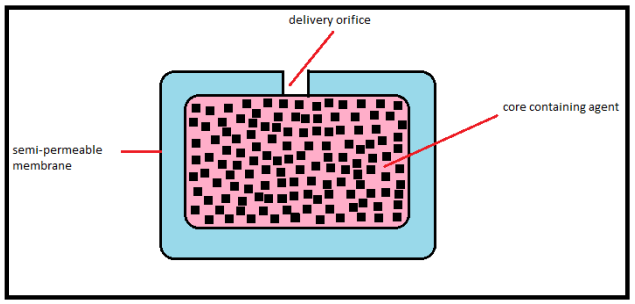

Figure 2: The elementary osmotic pump

Mechanism: Imbibes water through the SPM because of osmotic pressure gradient and forms the saturated medication solution inside the device. This increases the hydrostatic pressure inside the tablet forces the saturated drug solution through the hole present in film.

Advantages: suitable for delivery of drug having moderate water solubility. [(5).]

B. Multi chamber osmotic pump

I. Push –pull osmotic system (ppop):

Composition: they contain a few compartments isolated by versatile stomach upper compartment contains medicate with or without osmogen (sedate compartment nearly (60-80%) and lower compartment push compartment contain osmogen at 20-40%.it bilayer tablet coated semi permeable membrane.

Mechanism: when dosage form come in contact with aqueous environment, both compartments imbibe water simultaneously because lower compartment is avoid of any orifice, it expands and pushes the diaphragm into upper drug chamber, there by delivering the drug via the drug orifices.

Advantages: deliver both highly water soluble (oxybutynin hydrochloride) and practically insoluble.[6]

E.g. Procardia XL for nifidipine[12]

ii Osmotic pump with non expanding second chamber:

Composition: Multi-chamber devices comprise of systems containing a non – expanding second chamber.

Mechanism: purpose of second chamber is either dilution of drug solution leaving the device (particularly useful in handling drugs with high incidence of GI irritation) or simultaneous delivery of two drugs.

Advantages: Relatively insoluble drug can also be delivered.

2. Implantable osmotic pump

i. Rose and nelson osmotic pump

Composition: This pump is composed of three chambers: drug chamber, salt chamber, holding solid salt and water chamber.

Mechanism: a semi permeable membrane separates the salt from water chamber. The movement of water from

water chamber towards the salt chamber is influenced by difference in osmotic pressure membrane. Conceivably volume of salt chamber increase due to water flow which descends the latex diaphragm the salt and drug chambers, eventually the drug is pumped out of device. [7].

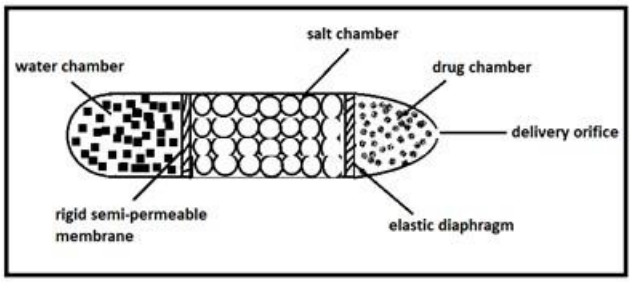

Figure 3: Rose and Nelson osmotic pump

ii. Higuchi Leeper pump

Composition:- Number of variation of rose nelson pump and these design have been described in U.S patents first series of simplifications of the rose nelson pump made by the Alza corporation Higuchi leeper pump has no water chamber, this pump contains a rigid housing, and a semipermeable 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.

Mechanism: Higuchi leeper pump has no water chamber, and activation of the device occurs after imbibition of water from the surrounding environment. This variation allows the device to be prepared loaded with drug and can be stored for long prior to use.

Application: - Higuchi-leeper pump is widely employed for veterinary use.

These pumps are intended to be implanted in animal to deliver the hormones.

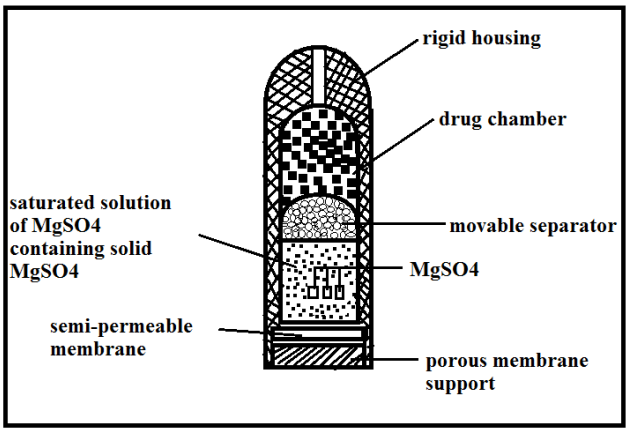

Figure 4: Higuchi Leeper pump

iii. Higuchi Theeuwes pump

Composition: - the rigid housing is consistent of a semi permeable membrane. The drug loaded in the device only prior to its application, which extends advantages for storage of device for longer duration.

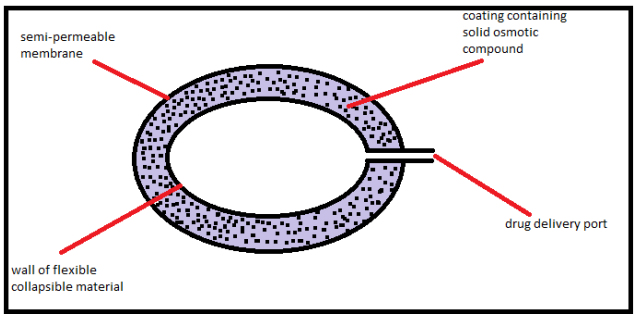

Figure 5: Higuchi Theeuwes pump

Mechanism: The release of the drug from device is governed by the salt used in the salt chamber and the permeability characteristics of outer membrane. Diffusional loss of the device is minimized by making the delivery port in shape of a long thin tube.

Application: They are used frequently as implantable controlled release delivery system in experiment studies requiring continuous administration of drug.[7, 8, 9]

iv. Implantable mini osmotic pump

Composition: It is composed of three concentric layers the drug reservoir, the osmotic sleeves and the rate controlling semi permeable membrane. The additional component called flow moderator is inserted into the body of the osmotic. The inner most compartment of drug reservoir which is surrounded by an osmotic sleeve, a cylinder containing high concentration of osmotic agent. The osmotic sleeve is covered by a semi permeable membrane. (figure no .6)

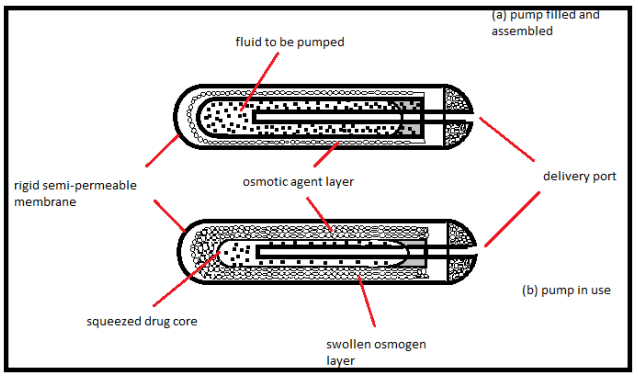

Figure 6: Theeuwes miniature osmotic pump

Mechanism: When the system is placed in aqueous environment water enters the sleeve through semi permeable membrane, compresses the flexible drug reservoir and displaces the drug solution through the flow moderator. These pumps are available with variety of delivery rates between .25to 10 ml per hour and delivery duration between one day and four week.[10]

3. Specific types

i. Controlled porosity osmotic pumps (CPOP)

Composition: - CPOPs are similar to EOP, the only difference being that the delivery orifice from which the

drug release takes place is formed by incorporation of a water-soluble additive in the coating.

Mechanism: After coming in contact with water, water soluble additives present in the coating dissolves and it results in an in-situ formation of a microporouse membrane as shown in figure. The release f drug takes place through this micrporous channels as shown in figure 7.

Advantages: Eliminates the need for a separate manufacturing step (creating an orifice using a laser drilling machine). Suitable for delivery of drugs having intermediate water solubility and extremes of water solubility by some modifications.[11, 12]

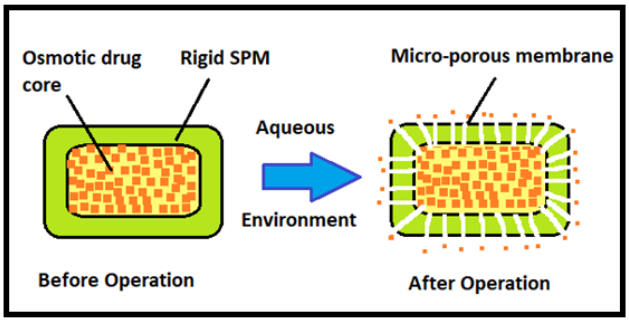

Figure 7: Controlled Porosity Osmotic Pump

ii. Osmotic bursting osmotic pump

Composition: This system is similar to an EOP expect delivery orifice is absent and size may smaller.

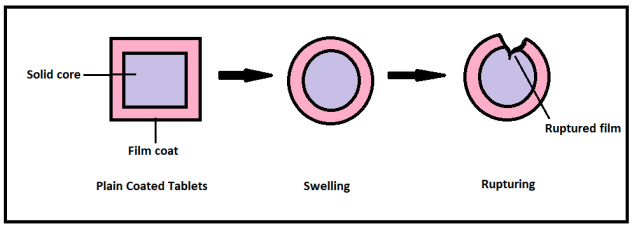

Figure 8: Osmotic Bursting Osmotic Pump

Mechanism: When it is placed in an aqueouseenvironment, water is imbibed by hydraulic pressure is built up inside untill the wall rupture and the content are released to the environment. Varying the thickness as well as the area the area semipermeable membrane can control release of drug.

Application:-This system is usefl to provide pulsated release. Liquid OROS:are designed todeliver drugsas liquid formulations and combine the benefits of extended release with high bioavailability.[8,12]

iii. Liquid OROS controlled release system (L-OROS)

a. Liquid OROS Soft Cap

b. Liquid OROS hard cap

a. Liquid OROS Soft Cap:-

Composition:-In soft cap, liquid drug formulationis present in a soft gelatin capsule, which is surrounded with the barrier layer, osmotic layer and the release rate-controlling membrane.[13]

b) Liquid OROS hard cap

Composition: In hard cap ,it consists of a liquid drug layer and anosmotic engine,all encased in a hard gelatin capsule and coatedwith semi permeable membrane.

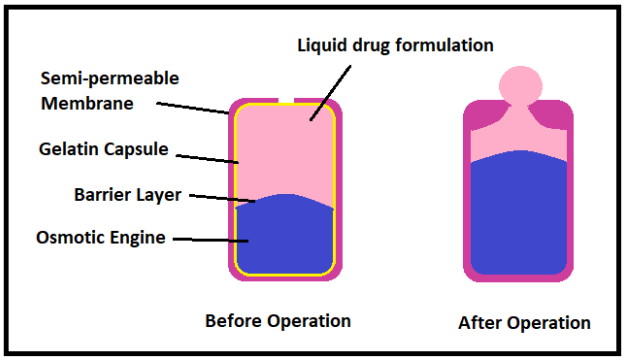

Figure 9: Liquid OROS hard cap

Mechanism:-The expansion of the osmotic layer result in the development of hydrostatic pressure, there by forcing the liquid formulation to break throughthe hydrated gelatin capsule shell at the delivery orifice.

Water is imbibed across the SPM,expanding the osmotic engine, which pushes against the barrier, releasing the drug through the delivery orifice.

Advantages:-To deliver APIs are as liquid formulations and combine the benefits of extended release with high bioavailability. Suitable for controlled delivery of lipophilic API[13].

iv. Sandwiched osmotic tablet (SOTS)

Composition:- Tablet core consisting of middle push layer and two attached drug layer is is coadted with a semi permeable membrane (SPM).

Mechanism: After coming in contact with the aqueouse environment, the middle push layer containing swelling agent sweels and thedrug is released from the delivery orifices.

Advantages: System delivers drug from two opposite orifices, rather in from the single orifice of the push- pull osmotic pump.(PPOP).[14]

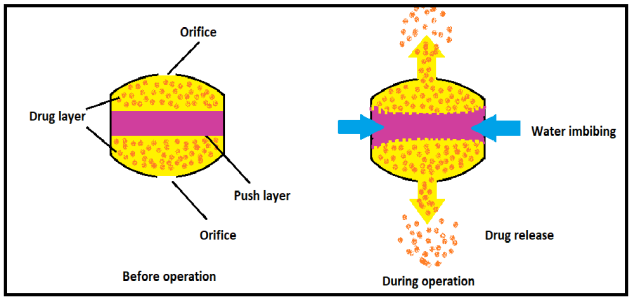

Figure 10: Sandwiched osmotic tablet

v. Monolithic osmotic system

Composition: The monolithic osmotic system consistsnof a simple dispersion of water-soluble agentin polymer matrix. The drug particles are encapsulated by polymers.

Mechanism: When the MOS comes in contact with the aqueous environment, the water imbibitions by the active agent takes place rupturing the polymer matrix capsule surrounding the drug , thus liberating drug to the outside environment. Initially this process occurs at the matrix in a serial fashion.

Advantages: these systems govern the zero order drug delivery kinetics. The principleenergy is osmotic pressure.[14]

vi. Telescopic capsule for delayed release

Composition:This device consists of two chambers, the first containsthe drug and an exit port, and the second contains osmotic engine .layer of wax –like material separates the two sections.

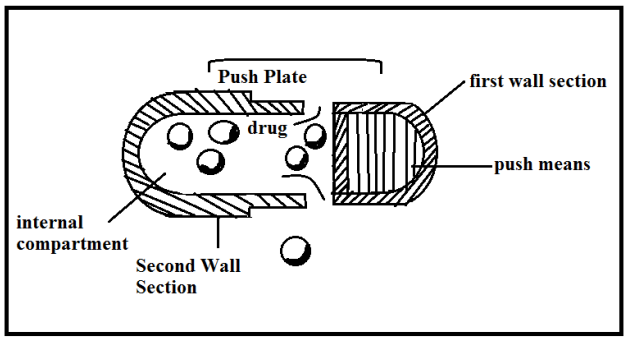

Figure 11: Telescopic capsule for delayed release

Mechanism: As fluid is imbibed the housing of the dispensing device, the osmotic engine expands and exerts pressure on the slidable connected first and second wall section[15].

EVALUATION

The evaluation parameters are as follow

1) Hardness: Tablet diameter & crushing strength of randomly selected tablet were determined using Scheleuniger tablet hardness tester.

2) Friability test: From each formulation, 20 tablet were placed in a friabilator (Roche friabilator) and subjected to rotations in 4 minutes. The tablet were then redusted are reweighed. The friability was calculated as percentage weight loss.

3) Effect of pH: These are done to see effect of pH on development of formulation so an *in vitro* study is carried out in different medias.

4) Effect of osmotic pressure: Release mechanism study is carried out at different osmotic pressure to see its effect on formulation.

5) *In-vitro* evaluation: *In vitro* release of drug from oral osmotic system is by conventional USP paddle & basket type of apparatus. Dissolution media is generally distilled water as well as simulated gastric fluid (for first 2-4 h)and intestinal fluids (for subsequent hours)have been used the standard specifications,

Which are as followed for oral controlled drug delivery system are equivalently applicable for oral osmotic pumps[16].

Marketed Study

In the market, there are thirty – one product has been developed and marketed based on oral osmotic drug system. all these products are under the therapeutic areas: cardiovascular (35%), neurological (25%) seasonal (25%) and metabolic disorders (15%). These products have been mainly developed by two companies; the former Alza corp. which was later acquired by Johnson & Johnson developed 20 products (53%).[17]

CONCLUSION

In the osmotic delivery system, 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. The osmotic drug delivery has travelled long way right from time discovery it undergoes various type of lift up. The osmotic drug delivery is slightly expensive drug delivery system still it is used because it attends to provide as good rate of drug release which tend to raise it acceptance in the pharmaceutical world.

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