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DESIGN OF CONTROL RELEASE OSMOTIC DRUG DELIVERY SYSTEM: A REVIEW

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ABSTRACT

The development of an ideal drug delivery system providing constant release of drug has been focus of much research, mainly with the objective of providing constant drug delivery during passage the GIT irrespective of variation in pH, surface tension, and viscosity as well as motility of GIT. Osmotic controlled drug delivery system is not influenced by different physiological factors with in the gut lumen and the release characteristic can be predicted easily from the drug and dosage form. Good product performance in osmotic system includes permeability of coating and drug release from the system. Osmotic pumps consist of an inner core containing drug and osmogens, coated with a semipermeable membrane. As the core absorbs water, it expands in volume, which pushes the drug solution out through the delivery ports. Osmotic pumps release drug at a rate that is independent of pH and hydrodynamics of the dissolution medium. The historical development of osmotic systems includes development of Rose-Nelson pump, Higuchi- Leeper pumps, Alzet and Osmet systems, elementary osmotic pump, and push-pull system applicability map and controlled porosity osmotic pump. This paper highlights the principle of osmosis, materials used for fabrication of pumps, types of pumps, advantages, disadvantages, and marketed products of this system.

Keywords: Osmosis, osmotic pressure, osmogen, semi permeable membrane,Osmotic pump, controlled-porosity osmotic pump tablet.

INTRODUCTION

Therapeutically active molecules for the treatment and prevention of new and existing diseases are currently being developed. Although pharmacological activity is the primary requirement for a molecule to be used as a therapeutic agent, it is equally important that the molecule reach its site of action, for this the term drug delivery is used. The conventional

drug therapy requires periodic doses of therapeutic agents. Conventional method of drug administration is effective but some drugs are unstable or toxic and have narrow therapeutic range and some drugs have solubility problems so to overcome these problems, controlled drug delivery system were introduced. The main goal of controlled drug delivery system is to improve the effectiveness of drug therapies. [(1)]

Scientists are pursuing the discovery and development of new molecules that have better absorptive and pharmacokinetic properties. Nevertheless, many existing and new molecules provide challenges of poor pharmacokinetics (e.g., short biological half-life) .Drug delivery systems such as oral controlled release dosage forms, are used to overcome these challenges. Among the various technologies used to control the systemic delivery of drugs, osmotic drug delivery is one of the most interesting and widely applicable.Osmotic drug delivery uses osmotic pressure of drug or other solute (called osmogents) for controlled delivery of drugs. Osmotic drug delivery has come a long way since Australian pharmacologists Rose and Nelson developed an implantable pump in 1955.This area of drug delivery has expanded into oral delivery and implants for humans and animals.[(3)]

In this form of novel drug delivery system (NDDS), an existing drug molecule can get a 'new life', thereby, increasing its market value, competitiveness, and patent life. Among the various NDDS available in market, oral controlled release (CR) system holds the major market share because of their obvious advantage of ease of administration and better patient compliance.[(4)]
CR delivery system provides desire concentration of drug at the absorption site allowing maintenance of plasma concentration within the therapeutic range and reducing the dosing frequency.A number of design options are available to control or modulate the drug release from a dosage form. Majority of per oral CR dosage forms fall in the category of matrix, reservoir, or osmotic systems.

However, factors like pH, presence of food, and other physiological factors may affect the drug release from conventional CR systems (Matrix and Reservoir). Osmotic system utilizes the principle of osmotic pressure for the delivery of drugs. Drug release from these systems is independent of pH and other physiological parameters to a large extent and it is possible to modulate the release characteristics by optimizing the properties of drug and system.[(1, 5)]
Alza corporation of USA (now merged with Johnson & Johnson, USA) was first to develop an oral osmotic pump and today also, they are leaders in this field with a technology named OROS.

Osmotic delivery devices have changed considerably since Rose and Nelson developed the first osmotic pump delivering drugs to animals. From complex implantable device to simple tablets, the extent of simplification and miniaturization has been remarkable. The osmotic delivery device of today not only delivers drugs with moderate solubility, but also is capable of delivering drugs with solubility extremes. Furthermore, devices that deliver drugs as liquids (to deliver insoluble drugs and to enhance permeability) and that dispense subsaturated solutions of drugs are noteworthy developments. [4]

Advantages of osmotic drug delivery systems[6, 7, 8]

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

1. They typically give a zero order release profile after an initial lag.
2. Deliveries may be delayed or pulsed if desired.
3. Drug release is independent of gastric pH and hydrodynamic condition
4. They are well characterized and understood. which is mainly attributed to the unique properties of semipermeable membrane (SPM) employed in coating of osmotic formulations.
5. The release mechanisms are not dependent on drug.
6. A high degree of *in-vitro* and *in-vivo* correlation (*ivivc*) is obtained in osmotic systems.
7. The rationale for this approach is that the presence of water in git is relatively constant, at least in terms of amount required for activation and controlling osmotically base technologies.
8. Higher release rates are possible with osmotic systems compared with conventional diffusion-controlled drug delivery systems.
9. The release from osmotic systems is minimally affected by the presence of food in gastrointestinal tract.
10. The release rate of osmotic systems is highly predictable and can be programmed by modulating the release control parameters.

Limitations of osmotic drug delivery systems

1. Special equipment is required for making an orifice in the system.
2. Residence time of system in the body varies with gastric motility and food intake.
3. It may cause irritation or ulcer due to release of saturated solution of drug.

Table.1:Comparison of delivery mechanism for osmotic tablet with other controlled release tablet technologies

	Osmotic	**Polymer Matrix (Diffusion, Swelling , Erosion)**	**Film[a]- Coated Tablet**
Mechanism for rate control	Osmotic Pump	Drug diffuse through viscous barrier (polymer matrix, hydrogel)	Drug diffusion through viscous barrier (polymer film coating)
Key formulation factors that control release	Membrane permeability	Polymer type[b]	polymer type[b]
	Membrane thickness	polymer mol wt.	polymer mol wt.
	Osmotic potential	polymer conc.	Coating thickness
Other factors that influence drug release			
Drug Loading	Little or no effect	Moderate Effect	Little or no effect
Tablets$(SA/V)^2$	Little or no effect	Moderate to large effect	Moderate to large effect
PH	No Effect	Large effect for ionizable	Moderate effect for ionizable
Hydrodynamics	No Effect	Large effect for ionizable	little or moderate effect

[a] Film refers to functional film coating (e.g., enteric coating)

[b]Type usually refers to the hydrophilic /hydrophobic nature of the polymer. For example, different grades of hydroxypropylmetylcellulose will achieve different release rates based on their ability to wet/interact with an aqueous environment

Osmosis [9,10,11]

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 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 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 solute (osmogent).

Principles of Osmosis

The first report of an osmotic effect dates to Abbenollet {1748}. But Pfeffer obtained the first quantitative measurement in 1877. In Pfeffer experiment a membrane permeable to water but

impermeable to sugar is used to separate a sugar solution from pure water. A flow of water then takes place into the sugar solution that cannot be halted until a pressure π is applied to the sugar solution. Pfeffer showed that this pressure, the osmotic pressure π of the sugar solution is directly proportional to the solution concentration and the absolute temperature. Within few years, Vant Hoff had shown the analogy between these results and ideal gas laws by the expression

$$\pi = Ø\ c\ RT$$

Where, π = Osmotic pressure,

Ø = 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 cm^2,

L = thickness,

Q = permeability

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.

Basic Components Of Osmotically Controlled Drug Delivery System (Osmotic Pumps) **[5, 8, 9]**

Osmotic pump essentially contain a drug and semipermeable membrane.in this case drug its self may act as an osmogen and shows good aqueous solubility (e.g. potassium chloride pumps).if the drug does not possess any osmogenic property, the osmogenic salt and others sugars can be incorporated in the formulation. Osmogens are freely water soluble and capable of producing osmotic pressure .Single osmogen can be used for the formulation and in some case combination of osmogen have been used apart from these essential components, other material such as hydrophilic and hydrophobic polymer and hydrogel (either swellabe or non swelllable nature).

Drug

Characteristics of drug candidate for osmotically controlled drug delivery

- Short biological half-life (2-6h)
- Highly potent drug
- Required for prolonged treatment e.g.various drug candidates such as Diltiazem HCl, Carbamazepine, Virapamil, Metoprolol,Oxprenolol, Nifedipine, Glipizide etc. are formulated as osmotic delivery.

Semi Permeable Membrane

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

Ideal Properties of Semi Permeable Membrane

The Semi Permeable Membrane must meet some performance criteria:

- The material must possess sufficient wet strength and wet modulus so as to retain its dimensional integrity during the operational lifetime of device.
- The membrane exhibit sufficient water permeability so as to retain water flux rate in the desired range. The water vapor transmission rates can be used to estimate water flux rates
- The reflection coefficient and leakiness of osmotic agent should approach the limiting value of unity. Unfortunately, polymer membranes that are more permeable to water are also, in general more permeable to osmotic agent.
- The membrane should also be biocompatible
- Rigid and non-swelling

- Should be sufficient thick to withstand the pressure within the device.
- The semi permeable membrane should be stable both to the outer and inner environment of the device.

.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 is commonly used as semipermeable polymer,it is available in different acetyl content of 32% and 38%, acetyl content is described by degree of substitution, cellulose triacetate having acetyl content of 35-44.8% are used and other ethyl cellulose and cellulose acetate butyrate, agar acetate, amylase triacetatebetaglucan acetate and polyacetals, Eudragitsetc are used.

Hydrophilic and hydrophobic polymers

- These polymers are used in the formulation development of osmotic systems containing matrix core. The selection of polymer is based on solubility of drug as well as the amount and rate of drug to be released from the pump.
- The highly water soluble compounds can be co-entrapped in hydrophobic matrices and moderately water soluble compounds can be co-entrapped in hydrophilic matrices to obtain more controlled release.
- The polymers are either swellable or nonswellablenature, mostly swellable polymers are used for the pumps containing moderately water-soluble drugs, since they increase the hydrostatic pressure inside the pump due to their swelling nature.
- The non swellable polymers are used in case of highly water soluble drugs. Ionic hydrogels such as sodium carboxymethyl cellulose are preferably used because of their osmogenic nature. Examples of hydrophilic polymers are hydroxy ethyl cellulose, carboxy methyl cellulose, hydroxyl propyl methyl cellulose, etc.
  Examples of hydrophobic polymers are ethyl cellulose, wax materials, etc.

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 wicking agent via Vander Waals interactions between the surface of wicking agent and adsorbed molecule.

- The function of wicking agent is to carry water to surfaces inside the core of tablet, thereby creating channels or a network of increased surface area. Materials, which suitably 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.

Solubilizing agent

Non-swellable solubilizing agents are classified in three groups,

1. Agents that inhibit crystal formation of drug,
2. A high HLB micelle-forming surfactant,
3. Citrate esters and their combinations with anionic surfactant,

   Above all combination of first and anionic surfactant are used such as PVP with SLS.

Osmotic agents

- Osmogents used for fabrication of osmotic dispensing device are inorganic or organic in nature. A water soluble drug by itself can serve the purpose of an osmogent.
- 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 actas 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 (alkalicarboxy methylcellulose) 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.

Types of osmotic agents

- **Inorganic water-soluble osmogents**

  Magnesium sulphate, Sodium chloride, Sodium sulphate, Potassium chloride, Sodium bicarbonate.

- **Organic polymer osmogents**

  Sodium carboxymethyl cellulose**,** Hydroxypropylmethyl cellulose**,** Hydroxyethylmethylcellulose**,** Methylcellulose**,** Polyethylene oxide**,** polyvinyl pyrollidine.

Table.2: Osmotic pressure of saturated solutions of common pharmaceutical solutes

Compounds of mixture	Osmotic pressure (atm)
Lactose-Fructose	500
Dextrose-Fructose	450
Sucrose-Fructose	430
Mannitol-Fructose	415
Sodium chloride	356
Fructose	335
Lactose-Sucrose	250
Potassium chloride	245
Lactose-Dextrose	225
Mannitol-Dextrose	225
Dextrose-Sucrose	190
Mannitol-Sucrose	170
Sucrose	150
Mannitol-Lactose	130
Dextrose	82
Potassium sulphate	39
Mannitol	38
Sodium phosphate tribasic. 12H2O	36
Sodium phosphate dibasic. 7 H2O	31
Sodium phosphate dibasic. 12 H2O	31
Sodium phosphate monobasic. H2O	28
Sodium phosphate dibasic. Anhydrous	21

Surfactants

- Surfactants are useful when added to wall forming material. They produce an integral composite that is useful for making the wall of device operative.
- The surfactant act by regulating the surface energy of material to improve their blending into the composite and maintain its integrity in environment of use during the drug release period.
- Typical surfactants are such as polyoxyethylenated glyceryl recinoleate, polyoxyethylenated castor oil having ethylene oxide, glyceryl laureates, glycerol etc.

Coating solvents

Solvents suitable for making polymeric solution that is used for manufacturing the wall of osmotic device include inert inorganic and organic solvents.

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

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, increase workability, flexibility of polymeric films. Generally from 0.001 to 50 parts of a plasticizer or a mixture of plasticizer are incorporated into 100 parts of wall forming materials.

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

Flux regulators

Delivery systems can be designed to regulate the permeability of the fluid by incorporating flux regulating agents in the layer. Hydrophilic substances such as polyethethylene glycols (300 to 6000 Da), polyhydric alcohols, polyalkylene glycols, and the like improve the flux, whereashydrophobic 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, can also be used for this purpose.

Pore forming agents

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.

The pore formers can be inorganic or organic and solid or liquid in nature. Like,

- Alkaline metal salts such as sodium chloride, sodium bromide, potassium chloride, etc.
- Alkaline earth metals such as calcium chloride and calcium nitrate
- Carbohydrates such as glucose, fructose, mannose, etc.

Development Of Osmotic Pump

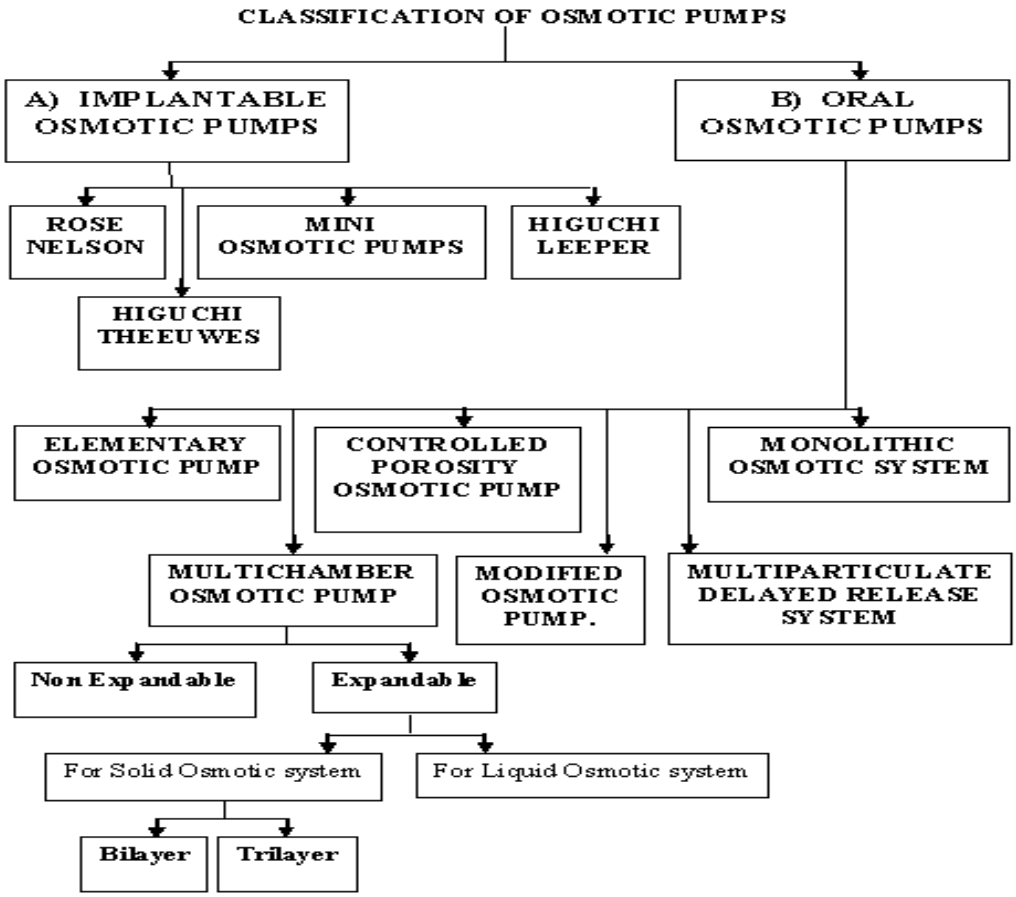
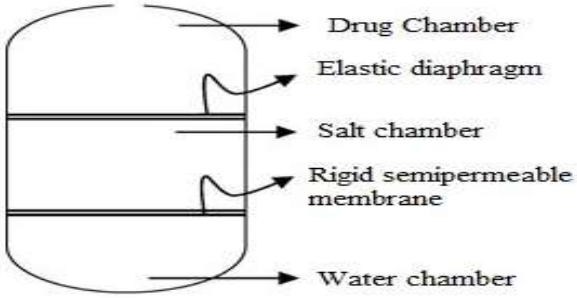


Fig.1: classification of osmotic pumps

Roes Nelson Pump[11,12,13]

In, 1955, two Australian physiologists reported the first osmotic pump. The pump consisted of three chambers a drug chamber with an orifice, a salt chamber with elastic diaphragm containing excess solid salt, and a water chamber. A semipermeable membrane separates the

drug and water chamber. The difference in osmotic pressure across the membrane moves water from water chamber in to the salt chamber. The volume of 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.



Higuchi Leeper Pump [12, 14, 15]

Design of Higuchi leeper pump described in fig.3 represents the first simplified version of alzet pump. It contains rigid housing and the semi permeable membrane, which is supported on a porous membrane. Rigid housing divides in two chambers by a movable separator. The benefit over rose nelson pump is that it does not have water chamber. And the device is activated by water imbibed from the surrounding environment. This means that the pump can be prepared loaded with drug and then stored for weeks and months prior to use.

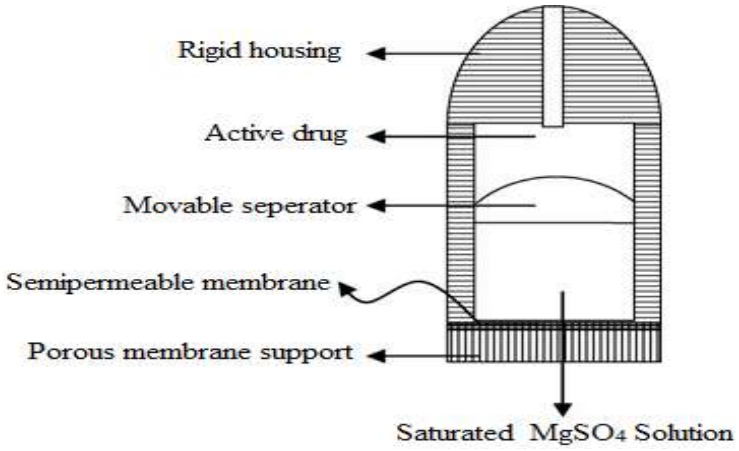


Fig.3: HiguchiLeeper pump.

Theeuwes Miniature Osmotic Pump [12, 16]

In early 1970s, Higuchi and Theeuwes developed another, even simpler variant of the rose – nelson pump. As with the Higuchi –Leeper pump, water to activate the osmotic action of the pump is obtained from the surrounding environment in the higuchi-theeuwes device shown in fig. however, the rigid housing is dispensed with and the membrane acts as outer casing of

pump. This membrane is quite sturdy and is strong enough to withstand the pumping pressure developed inside the device. The device is loaded with desired drug prior to use.

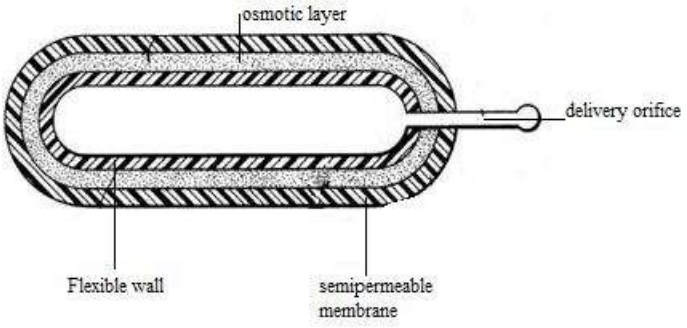


Fig.4: Theeuwes Miniature Osmotic Pump.

When the device is placed in an aqueous environment ,release of the drug follows a time course set by the salt used in the salt chamber and the preferably of the outer membrane casing . Most of higuchi-theeuwes pumps use a dispersion of solid salt in a suitable carrier for the salt chamber of device.

Applicability Of Osmotic Tablet Technology

The consideration of dose and solubility is a starting point when evaluating a drug candidate for controlled release using osmotic pump tablet technologies. The delivery volume, is defined as the volume of water required to dissolved the dose, is a useful parameter assessing the tablet technology is most appropriate and gives an indication of a challenge associated with successful development of CR tablet . The delivery volume Dv is defined by equation given below, Where the solubility is simply the solubility in aqueous media. Clearly the solubility can be different as a function of pH for ionizable drugs, and for some drug may depend on the presence of micelles and surfactant.

$$Dv = \text{dose (mg)} / \text{solubility (mg /ml)}$$

For the purpose of selecting an osmotic tablet technology for CR delivery knowing the solubility of drug in unbuffered water, intestinal media buffered between 6.5 and 7.5 or to a pH that can practically be achieved in tablet core protected by a semipermeable coating all are useful for measure of solubility. when the delivery volume is on the order of 1ml, It is still possible to dissolve the dose within the osmotic tablet core , and it may allow other types of osmotic tablet technologies (e.g. asymmetric membrane and elementary) when the dose volume exceeds 1ml , the entire dose cannot be dissolved in 1-2ml of water that is typically imbibed in tablets of an acceptable size (i.e. 1g or less in weight).with increasing dose

volume , the portion of the dose will be delivered as a suspension from an osmotic tablet increases.

The dose volume can also give an indication of how much of the dose can be expected to be absorbed in the lower based on solubility. This is particularly important when the delivery of the drug must be sustained more than 4-6 h and therefore require some portion of dose to be delivered to the colon where the amount of water is very limited. a high dose volume (i.e., > 100ml) in combination with a long-duration osmotic tablet (i.e. 16 h) indicates that absorption may be delivered to the colon where the volume of available water is on the order of 50 ml or less. Some empirically based guidelines have been reported to suggest that as the dose volumes approach 1000 ml and higher, a means to enhance drug solubility will be required to promote absorption in the lower GI tract, even for relative short release duration (i.e., 4-6 h) in figure.7 the applicability map for choosing an osmotic tablet technology based on dose and solubility is shown in fig.7

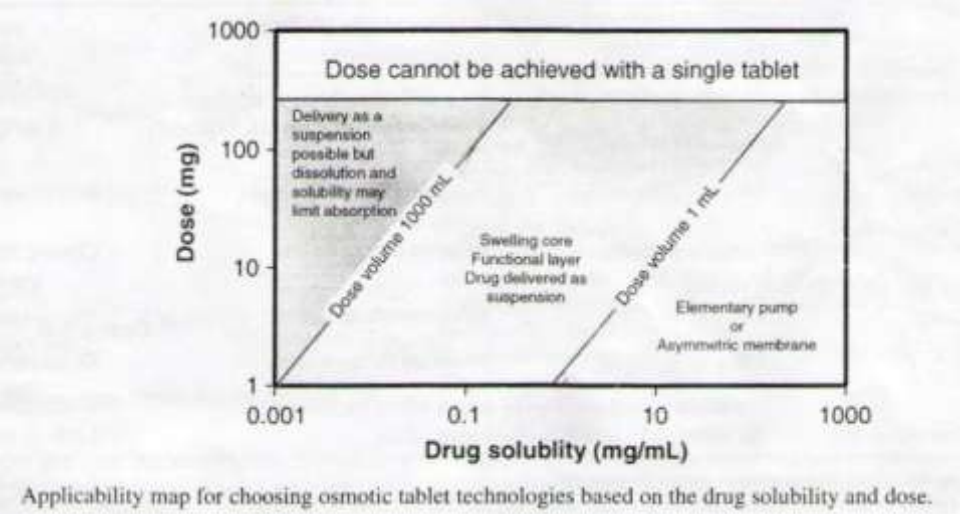


Fig.5: Applicability map for choosing osmotic tablet technologies based on the drug solubility and dose.

TYPES OF ORALOSMOTIC PUMPS

Based on their design and the state of active ingredient, Oral osmotic systems can be classified as follows:

Osmotic delivery systems for solids

- **Single chamber osmotic pump:** Elementary osmotic pump
- **Multi chamber osmotic pump:** Push pull osmotic pump, Osmotic pump with non-expanding second chamber

- **Specific types:** Controlled porosity osmotic pump, Osmotic bursting osmotic pump, Liquid OROS, Delayed Delivery Osmotic device, Telescopic capsule, Oros ct (colon targeting), sandwiched oral therapeutic system, Osmotic pump for insoluble drugs, Monolithic osmotic system and OSMAT

Elementary osmotic pump (EOP)[2, 9, 10, 18, 23]

This was introduced in 1970s to deliver drug at zero order rate for prolonged periods, and is minimally affected by environmental factors such as pH or motility. The tablet consists of an

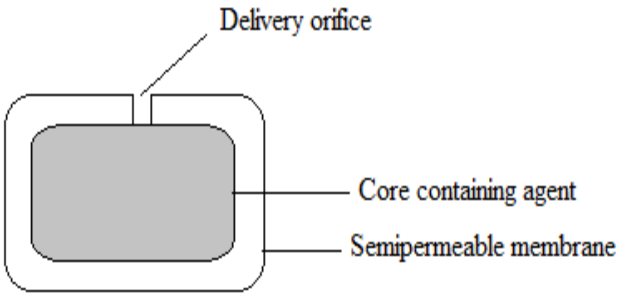


Fig.6: Elementary osmotic pump.

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 is that it is only suitable for the delivery of water soluble drugs.

Limitation of EOP

- SPM should be 200-300μm thick to withstand pressure
- Thick coatings lowers the water permeation rate
- Applicable mostly for water soluble drugs

Push–Pull Osmotic Pump (PPOP) [23]

The two-layer push–pull osmotic tablet system appeared in 1980s. Push pull osmotic pump is a modified elementary osmotic pump through, which it is possible to deliver both poorly and highly water soluble drugs at a constant rate. The push–pull osmotic tablet consists of two layers,one containing the drug and the other an osmotic and expandable agent. A semipermeablemembrane that regulates water influx into both layers surrounds the system. While the push–pullosmotic tablet operates successfully in delivering water-insoluble drugs,

it has a disadvantage that thecomplicated laser drilling technology should be employed to drill the orifice next to the drugcompartment.

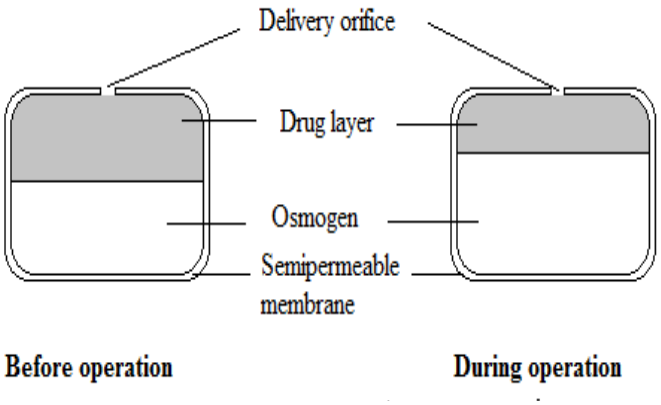


Fig.7: Push–Pull Osmotic Pump.

Controlled Porosity Osmotic Pump [19, 20, 21, 22, 23]

A controlled porosity osmotic pump-based drug delivery system Unlike the elementary osmotic pump (EOP) consists of an osmotic core with the drug surrounded by a semipermeable membrane drilled with a delivery orifice, controlled porosity of membrane is accomplished by the use of different channeling agents in the coating. The CPOP contains water soluble additives in coating membrane, which after coming in contact with water; dissolve resulting in an in-situ formation of a microporous membrane. Then the resulting membrane is substantially permeable to both water and dissolved solutes and the mechanism of drug release from these systems was found to be primarily osmotic, with simple diffusion playing a minor role.

Drug delivery from asymmetric membrane capsule is principally controlled osmotic pressure of the core formation. In-situ formed delivery orifice in the asymmetric membrane in mainly responsible for solubilization in the core for a drug with poor water solubility.

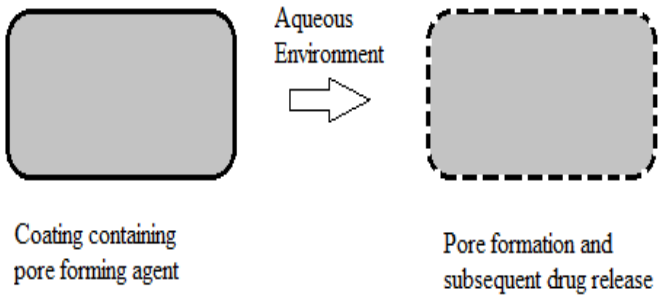


Fig.8: Controlled porosity osmotic pump.

Osmotic delivery systems for liquids. [24, 25, 10, 26]

Active ingredients in liquid form are difficult to deliver from controlled release platforms becausethey tend to leak in their native form. Therefore, liquid active agents typically are enclosed in a soft gelatin capsule, which is surrounded by an osmotic layer that, in turn, is coated with a semipermeable membrane. When the system takes up water from its surroundings, the osmotic layer squeezes the innermost drug reservoir. The increasing internal pressure displaces the liquid from the system byRupturing soft gelatin capsule.

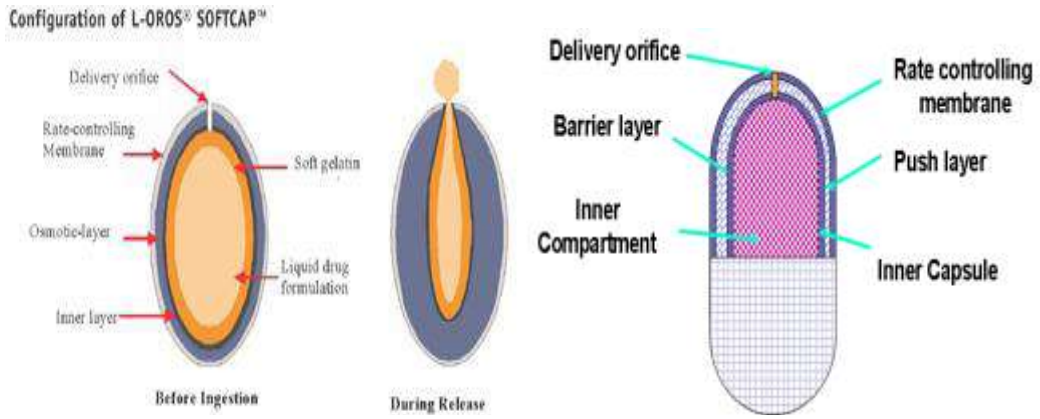


Fig.9: L-Oros system of a softcap™ and Hardcap™

One type of L-Oros system consists of a soft gelatin capsule (softcap™) surrounded by a barrier layer, an osmotic push layer, and a semipermeable membrane. As with other Oros system, drug is released through a delivery orifice in the semipermeable membrane. Another type of L-Oros system consists of a hard gelatin capsule (Hardcap™) containing a liquid drug layer, a barrier layer, and a push layer surrounded by a semipermeable membrane. The L-Oros Hardcap system was designed to accommodate more viscous suspensions with higher drug loading than would be possible with Softcap design.

Osmotic bursting osmotic pump[23]

This system is similar to an EOP except delivery orifice is absent and size may be smaller. When it is placed in an aqueous environment, water is imbibed and hydraulic pressure is built up inside until the wall rupture and the content are released to the environment. Varying the thickness as well as the area the semipermeable membrane can control release of drug. This system is useful to provide pulsated release.

Telescopic capsule for delayed release[9,26]

This device consists of two chambers; the first contains the drug and an exit port, and second contains an osmotic engine. A layer of wax like material separates the two sections. To assemble the delivery device, the desired active agent is placed into one of the sections by manual or automated fill mechanism. The bilayer tablet with the osmotic engine is placed into a completed cap part of the capsule with the convex osmotic layer pointed in to the closed end of cap and the barrier layer exposed towards cap opening. The open end of the filled vessel is fitted inside the open end of cap, and the two pieces are compressed together until the cap, osmotic bilayer tablet and vessel fit together tightly. As fluid is imbibed the housing of dispensing device, the osmotic engine expand and exerts pressure on the slidable connected first and second wall sections. During the delay period the volume of reservoir containing the active agent is kept constant, therefore a negligible pressure gradient exists between the environment of use and interior of reservoir. As a result, the net flow of environmental fluid driven by pressure enter thereservoir minimal and consequently no agent is delivered for the period.

OROS-CT(10, 25, 26 27)

OROS-CT (Alza corporation) is used as a once or twice a day formulation for targeted delivery of drugs to the colon. The OROS-CT can be a single osmotic agent or it comprised of as many as five to six push pull osmotic units filled in a hard gelatin capsule. After coming in contact with gastric fluids, gelatin capsule dissolves and the enteric coating prevents entry of fluids from stomach to the system as the system enters into the small intestine the enteric coating dissolves and water is imbibed into the core thereby causing the push compartment to swell. At the same time flowable gel is formed in the drug compartment, which is pushed out of the orifice at a rate, which is precisely controlled, by the rate of water transport across the semi permeable membrane. Incorporation of cyclodextrin-drug complex has also been used as an approach for delivery of poorly water soluble drugs from the osmotic systems. Ex. Sulfobutylether-Bcyclodextrin sodium salt serves as a solubilizer and osmotic agent.

Sandwiched Osmotic Tablets (SOTS)[9, 10, 24, 25]

In this a tablet core composed of polymeric push layer sandwiched between two drug layers with two delivery orifices. When placed in the aqueous environment the middle push layer containing the swelling agent swells and drug is released from the two orifices situated on

opposite sides of and thus SOTS can be suitable for drugs prone to cause local irritation of gastric mucosa.

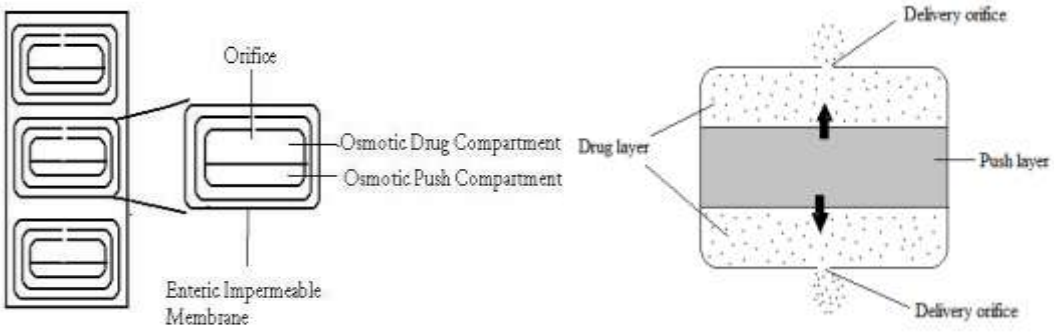


Fig.10: Sandwiched osmotic tablets

Longitudinally compressed tablet (LCT) multilayer formulation[23]

LCT multilayer formulation is the advanced design. As with the push-pull system it consists of an osmotic push layer and can be configured to contain several drug layers. The opinion of multiple drug layers provides increased flexibility and control over the pattern of release of medication from the system, as opposed to single layer used in the push-pull system, which can deliver a drug only in a zero order fashion. For example, two drug layers could be formulated with different drug concentration to provide modulation in the release rate profile. As with the push-pull formulation, water is absorbed through the exposed semipermeable tablet shell, expanding the push compartment and releasing the drug primarily from the first compartment through the laser drilled orifice at a predetermined controlled rate. After that most of the drug release begins from the second compartment at a different rate. Varying the relative viscosity and hydrophilicity of the drug layer components one can control the amount of mixing between the multiple drug layers. This allows even greater flexibility to achieve the target release profile.

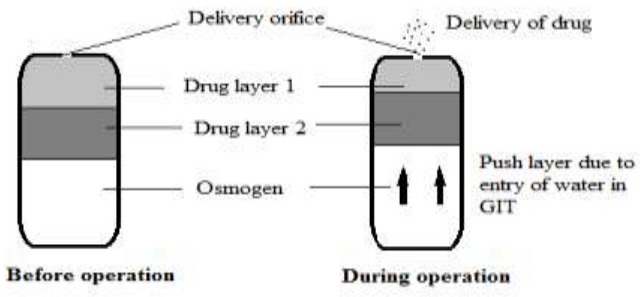


Fig.11:Multilayer osmotic pump

The LCT multilayer formulation can also be formulated with different drugs in different layers to provide combination therapy. Similar to the push-pull system, drug delivery by the

LCT multilayer formulation can be unaffected by gastric pH, gut motility and presence of food, depending on where in GI tract the drug is released.

Multiparticulate Delayed Release System[23,25,28]

Pellets containing drug with or without osmotic agent are coated with semi permeable membrane which on contact with aqueous environment results in penetration of water in core and forms a saturated solution of soluble component. The osmotic pressure difference results in rapid expansion of membrane, which leads to the formation of pores.

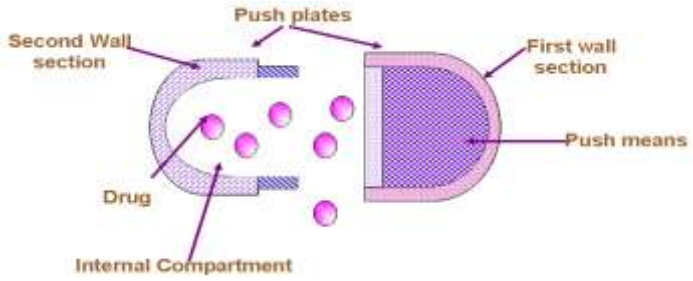


Fig.12: Multiparticulate Delayed Release System

Pulsatile delivery system [25, 28]

Pulsatile systems are gaining a lot of interest as they deliver the drug at the right site of action at right time and in right amount, thus providing spatial and temporal delivery and increasing patient compliance. These systems are designed according to the circadian rhythm of body. The principle rationale for the use of pulsatile release is for drugs where a constant drug release, i.e., a zero order release is not desired. The release of drug as a pulse after a lag time has to be designed in such a way that a complete and rapid drug release follows the lag time. This type of tablet system consists of core coated with two layer of swelling and rupturable coatings herein spray dried lactose and microcrystalline cellulose is used in drug core and then core coated with swelling polymer croscarmellose sodium and an outer rupturable layer of ethylcellulose. Pulsatile systems can be classified into single and multiple-unit systems. Single-unit systems are formulated either as capsule-based or osmosisbased systems. Single-unit systems are designed by coating the system either with eroding/soluble or rupturable coating. In multiple-unit systems, however, the pulsatile release is induced by changing membrane permeability or by coating with a rupturable membrane.

CREATION OF DELIVERY ORIFICE

Osmotic delivery systems contain at least one delivery orifice in the membrane for drug release. The size of delivery orifice must be optimized in order to control the drug release

from osmotic systems. On the other hand, size of delivery orifice should not also be too large; otherwise, solute diffusion from the orifice may take place. If the size of delivery orifice is too small, zero-order delivery will be affected because of development of hydrostatic pressure within the core. This hydrostatic pressure may not be relieved because of the small orifice size and may lead to deformation of delivery system, thereby resulting in unpredictable drug delivery. Optimum orifice diameter is in the range of 0.075–0.274 mm. At orifice size of 0.368mm and above, control over the delivery rate is lost. Delivery orifices in the osmotic systems can be created with the help of a mechanical drill.[29] Laser drilling is one of the most commonly used techniques to create delivery orifice in the osmotic tablet.[30] Laser beam is fired onto the surface of tablet that absorbs energy ofbeam and gets heated ultimately causing piercing of wall and, thus forming orifice. It is possible to control the size of passageway by varying the laser power, firing duration (pulse time), thickness of the wall, and dimensions of beam at the wall. In some of the oral osmotic systems, there is in situ formation of delivery orifice. The system described consists of incorporation of pore-forming agents into the coating solution. Pore-forming agents are water soluble: upon contact with the aqueous environment, they dissolve in it and leach out from membrane, creating orifice.[31]Indentation that is not covered during the coating process Indentation is made in core tablets by using modified punches having needle on upper punch. This indentation is not covered during coating process which acts as a path for drug release in osmotic system.[32]

Factors Affecting Drug Release Rate From Osmotic Controlled Drug Delivery System[5, 9, 25]

Solubility: APIs for osmotic delivery should have water solubility in the desired range to get optimize drug release. However, by modulating the solubility of these drugs within the core, effective release patterns may be obtained for the drugs, which might otherwise appear to be poor candidate for osmotic delivery. Various Solubility-modifying approaches should be used to modify the solubility.

- Use of swellable polymers: vinyl acetate copolymer, polyethylene oxide have uniform swelling rate which causes drug release at constant rate. [33]
- Use of wicking agents: These agents may enhance the surface area of drug with the incoming aqueous fluids. e.g. colloidal silicon dioxide, sodium lauryl sulfate, etc. Ensotrol® technology uses the same principle to deliver drugs via osmotic mechanism.[34]
- Use of effervescent mixtures: Mixture of citric acid and sodium bicarbonate which creates pressures in the osmotic system and ultimately controls the release rate. [35]

- Use of cyclodextrin derivatives: They are known to increase solubility of poorly soluble drugs. The same phenomenon can also be used for the osmotic systems.[36]
- Use of alternative salt form: Change in salt form of may change solubility.
- Use of encapsulated excipients: Solubility modifier excipient used in form of mini-tablet coated with rate controlling membrane.[37]
- Resin Modulation approach: Ion-exchange resin methods are commonly used to modify the solubility of APIs. Some of the resins used in osmotic systems are Poly (4-vinyl pyridine), Pentaerythritol, citric and adipic acids. [38]
- Use of crystal habit modifiers: Different crystal form of the drug may have different solubility, so the excipient which may change crystal habit of the drug can be used to modulate solubility. [39]
- Co-compression of drug with excipients: Different excipients can be used to modulate the solubility of APIs with different mechanisms like saturation solubility, pH dependent solubility. Examples of such excipients are organic acids, buffering agent, etc.[40,41]

  Osmotic pressure: The next release-controlling factor that must be optimized is the osmotic pressure gradient between inside the compartment and the external environment. [30]

  Size of delivery orifice: To achieve an optimal zero order delivery profile, the cross sectional area of the orifice must be smaller than a maximum size to minimize drug delivery by diffusion through the orifice. Furthermore, the area must be sufficiently large, above a minimum size to minimize hydrostatic pressure build up in the system. The typical orifice size in osmotic pumps ranges from 600µ to 1 mm. Methods to create a delivery orifice in the osmotic tablet coating are:

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

Coating membrane: Release rate affected by

- type and nature of membrane forming polymer,
- thickness of the membrane,
- Presence of other additives (type and nature of plasticizer, flux additives, etc.). Membrane permeability can be increased or decreased by proper choice of membrane-forming polymers and other additives.

Evaluation Of The Osmotically Controlled Delivery System [42, 43, 44, 45, 48]

Evaluation of the Osmotic tablet

a) Weight Variation
b) Hardness
c) Friability
d) Thickness
e) Drug content
f) Dissolution
g) Pore Diameter
h) Coating Thickness

In vitro evaluation

The in vitro release of drugs from oral osmotic systems has been evaluated by the conventional USP paddle and basket type apparatus. The dissolution medium 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 followed for the oral controlled drug delivery systems are equivalently applicable for oral osmotic pumps.[50]

In vivo evaluation

In vivo evaluation of oral osmotic systems has been carried out mostly in dogs. As the environment in the intestinal tract of the dog is very similar to that of human beings terms of both pH and motility, dogs have been used widely for in vivo delivery rate measurement of drugs from osmotically controlled oral drug delivery systems and also to establish in vitro in vivo correlation. Monkeys can also be used but in most of the studies the dogs are preferred.

Curve fitting analysis[47, 48, 49]

a) Zero order release kinetic
b) First order release kinetic

Table.2: Osmotic drug delivery products available in Market

Trade Name	Company name	Active ingredient	Design system	Dose	Use
Alpress LP	Alza corporation	Prazosin	Push -Pull	2.5 - 5 mg	For the treatment of hypertension
DynaCirc CR	Alza	Isradipine	Push -Pull	5 mg	Used in the treatment of hypertension
Efidac 24	Novartis /Pfizer / Alza	Chlorpheniramine maleate	Elementary Pump	4 mg IR, 12 mg CR	Used as antihistamine.Chlorpheniramine is used to treat sneezing; runny nose; itching, watery eyes; hives; rashes; itching; and other symptoms of allergies and the common cold.
Cyclobenzaprine OROS	Merck / Alza	Cyclobenzaprine			Anti-arthritis drug, Pain relief
Osmosin	Merck /Alza	Indomethacin		100mg	Used in treatment of osteoarthritis, fever, pain, stiffness and swelling.
Glucotrol XL	Pfizer / Alza	Glipizide	Push - Pull	5, 10 mg	For the control of hyperglycemia in patients with non-insulin-dependent diabetes
Cardura XL	Pfizer Inc.	Doxazosin	Push -Pull	4, 8 mg	For the treatment of hypertension
Acutrim	AlZA	Phenylpropanolamine	Elementary pump	75 mg	For the treatment the congestion associated with allergies, hay fever, sinus irritation, and the common cold.
Chronogesic TM	Alza	Sufentanil	Implantable osmotic systems		Anesthetics,Intravenous; Narcotics; Adjuvants, Anesthesia; Analgesics, Opioid; Opiate Agonists
Efidac24 Brompheniramine & Pseudopheniramine	Alza	Brompheniramine Norpseudoephidrine	Elementary osmotic pump	16mg,240 mg	Used to treat nasal or sinus congestion caused by the common cold, sinusitis,and hay fever ,in ear congestion and respiratory allergies.

Ditropan XL	AlZA	Oxybutnin chloride	Push -Pull	5, 10 mg	For the once daily treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency
Covera HS	Pfizer /Alza	Verapamil	Push -Pull with time delay	180, 240 mg	For the management of hypertension and angina
Procardia XL	Pfizer / Alza	Nifedipine	Push - Pull	30, 60, 90 mg	Calcium channel blocker. By blocking calcium, nifedipine relaxes and widens the blood vessels. It is used to treat high blood pressure and chest pain (angina).
Minipress XL	Pfizer / Alza	Prazocine	Elementary pump	2.5, 5 mg	Antihypertensive Agents; Alpha-adrenergic Blocking Agents
Concerta	Alza	Methylphenidate	Implantable osmotic systems	18, 27, 36, and 54 mg	A psychostimulant drug approved for treatment of attention-deficit hyperactivity disorder, Postural Orthostatic Tachycardia Syndrome, and narcolepsy
Teczem	Merck & Hoechst Marion	Enalapril and Diltiazem		180mg/ 5mg	Used in the treatment of hypertension , lower high blood pressure
Volmax	Alza	Sabutamoll	Elementary pump	4, 8 mg	For relief of bronchospasm in patients with reversible obstructive airway disease
Viadur	Alza	Leuprolide acetate	Implantable osmotic systems	65 mg, 72mg	Used in the treatment of advanced prostate cancer and in uterine fibroids and endometriosis
Invega	Alza	Paliperidone	Push -Pull	3, 6, 9 mg	for the treatment of schizophrenia

CONCLUSION

Osmotic pumps are one of the systems for controlled drug delivery. Osmotic drug delivery systems typically consist of a drug core containing osmogen that is coated with a semipermeable membrane. This coating has one or more delivery ports through which a solution or suspension of the drug is released over time. Drug delivery from these systems, to a large extent, is independent tract. Because of their unique advantages over other types of dosage forms, osmotic pumps from a class of their own among the various drug delivery technologies, and a variety of products based on this technology are available on the market.

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