

A REVIEW ON ORAL OSMOTICALLY DRIVEN SYSTEMS

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ABSTRACT

In recent years, oral controlled release (CR) system is most acceptable dosage form by the patients. Drugs having short biological half-life and poor water solubility are the suitable candidate for development of CR system. Research revealed that conventional matrix or reservoir type formulations exhibit bioavailability issues due to gastric pH variations and is also affected by the hydrodynamic conditions of the body. Introduction of osmotically controlled oral drug delivery systems (OCDDS) overcame these issues. OCDDS utilize osmotic pressure for controlled delivery of active agent(s). Drug delivery from these systems is independent of the physiological factors of the gastrointestinal tract and these systems can be utilized for systemic as well as targeted delivery of drugs. The release of drug(s) from osmotic systems follows zero order. It is mainly governed by various formulation factors such as solubility and osmotic pressure of the core component(s), size of the delivery orifice, and nature of the rate-controlling membrane. The present review highlights an overview of OCDDS. Further, the challenges of these technologies and its future perspective are also discussed at length.

Keywords: Osmotic pumps, Osmosis, Zero-order, Semipermeable membrane, Osmotic agent.

INTRODUCTION

Novel drug delivery systems (NDDS) are the key area of pharmaceutical research and development. The reason is relatively low development cost and time required for introducing a NDDS (\$20-50 million and 3-4 years, respectively) as compared to new chemical entity (approximately \$500 million and 10-12 years, respectively). The focus in NDDS includes design of NDDS for new drugs on one hand and on the other NDDS for established drugs to enhance commercial viability [1].

During the past three decades significant advances have been made in the area of NDDS. Among the various NDDS available in market, controlled drug delivery system has taken major role in the pharmaceutical development. This is due to improved patient convenience and compliance, reduction in fluctuation in steady state plasma level so decrease intensity of local or systematic side effects and increase safety margin of high potency drugs. In controlled release (CR) systems, there is maximum utilization of drug enabling reduction in total amount of dose administered and possibility of delivering drugs having short biological half-life[2].

Various designs are available to control or modulate the drug release from a dosage forms. Majority of oral CR dosage forms fall in the category of matrix, reservoir or osmotic systems. Conventional matrix or reservoir type formulations exhibit problem of bioavailability fluctuations due to gastric pH variations. Moreover, the release of drugs from these systems is affected by the hydrodynamic conditions of the body.

Osmotically controlled drug delivery systems (OCDDS) is one of the most promising drug delivery technologies that use osmotic pressure as a driving force for controlled delivery of active agents[3]. Drug release from OCDDS is independent of pH and hydrodynamic conditions of the body because of the semipermeable nature of the rate-controlling membrane and the design of delivery orifice used in osmotic systems, so a high degree of *in vitro/in vivo* correlation is achieved. It is also possible to obtain higher release rates through these systems than through other diffusion-based systems[4, 5]. There are over 240 patented osmotic drug delivery systems. They are also known as GITS (gastro-intestinal therapeutic system) [6] and today, different types of osmotic pumps, of various drugs, are available in the market to fulfil patient's need and requirement [7, 8]. This review mainly focuses on the theoretical aspects, basic components of OCDDS, factors affecting OCDDS, different technologies, marketed products and future aspects of OCDDS.

Key Milestones in OCDDS development

Rose-Nelson Pump

Rose and Nelson, the Australian scientists, were initiators of osmotic drug delivery. In 1955, they developed an implantable pump, which consisted of three chambers: a drug chamber, a salt chamber contains excess solid salt, and a water chamber. The drug and water chambers are separated by rigid semipermeable membrane. The design and mechanism of this pump is comparable to modern push-pull osmotic pump. The major disadvantage of this pump was the water chamber, which must be charged before use of the pump[9].

Higuchi-Leeper Pump

Several simplifications in Rose-Nelson pump were made by Alza Corporation in early 1970s. The Higuchi-Leeper pump is modified version of Rose-Nelson pump. It has no water chamber, and the device is activated by water imbibed from the surrounding environment. The pump is activated when it is swallowed or implanted in the body. This pump consists of a rigid housing, and the semipermeable membrane is supported on a perforated frame. It has a salt chamber containing a fluid solution with excess solid salt[10-11].

Higuchi-Theeuwes Pump

In the 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, however, the rigid housing is dispensed with and the membrane acts as the outer casing of the pump. This membrane is quite sturdy and is strong enough to withstand the pumping pressure developed inside the device. The device is loaded with the desired drug prior to use. 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 permeability of the outer membrane casing. Most of the Higuchi-Theeuwes pumps use a dispersion of solid salt in a suitable carrier for the salt chamber of the device[12].

Advantages of Osmotic Drug Delivery System[13]:

Apart from the general advantages of controlled drug delivery systems, osmotic pumps have certain unique advantages, as follows:

1. Delivery of drug from osmotic pumps can be designed to follow true zero-order kinetics.
2. Delivery may be delayed or pulsed, if desired.

3. Drug release from osmotic pumps is independent of the gastric pH and hydrodynamic conditions of the body.
4. Higher release rates are possible from osmotic systems than with conventional diffusion based drug delivery systems.
5. The delivery rate of drug(s) from these systems is highly predictable and programmable by modulating the release control parameters.
6. A high degree of *in vitro/in vivo* correlation can be obtained from osmotic pumps.
7. Drug release from the osmotic systems is minimally affected by the presence of food.

Basic Concepts

Principle of Osmosis

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[14].

Delivery Rate

The OCDDS consists of an osmotic core containing drug and an osmogen surrounded by a semipermeable membrane with an aperture. A system with constant internal volume delivers a volume of saturated solution equal to the volume of solvent uptake in any given time interval. Excess solids present inside a system ensure a constant delivery rate of solute. The rate of delivery generally follows zero-order kinetics and declines after the solute concentration falls below saturation[15]. The solute delivery rate from the system is controlled by solvent influx through the semipermeable membrane.

The osmotic flow of the liquid depends on the osmotic and hydrostatic pressure differences across the semipermeable membrane of the system. This phenomenon is the basic feature of nonequilibrium thermodynamics, which describes the volume flux across the semipermeable membrane[16].

Formulation Considerations of OCDDS

Generally OCDDS consists of two parts: One of this is core and another is semipermeable membrane (coating). Core of OCDDS consists of drugs, osmotic agents, hydrophilic and hydrophobic polymers, flux regulating agents, wicking agents, while coating includes polymer, coating solvent, plasticizers and poreforming agents.

Drugs

Drugs which have short biological half-life (2-6hr) and which are used for prolonged treatment are ideal candidate for osmotic systems. Various drug candidates such as Diltiazem hydrochloride[17], Carbamazepine, Metoprolol[18], Oxprenolol, Nifedipine[19,20], Glipizide[21], etc are formulated as osmotic delivery.

Osmotic Agents[22]

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. Different type of osmogens can be used for such systems are categorized in table 1.

Hydrophilic and Hydrophobic Polymers

These polymers are used in the formulation development of osmotic systems for making drug containing matrix core. The selection is based on the solubility of the drug as well as the amount and rate of drug to be released from the pump.

The polymers are of either swellable or non-swellable nature. 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[23].

Flux Regulating agents

Delivery systems can be formulated to regulate the permeability of the fluid by incorporating flux-regulating agents in the layer. Hydrophilic substances improve the flux, whereas hydrophobic materials tend to decrease the flux. Insoluble salts or insoluble oxides, which are substantially water-impermeable materials, also can be used for this purpose[23].

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.

The function of wicking agent is to carry water to surfaces inside the core of the tablet, thereby creating channels or a network of increased surface area[23].

Semipermeable Membrane[22]

An important part of the osmotic drug delivery system is the semipermeable membrane housing. Therefore, the polymeric membrane selection is important to the osmotic delivery formulation. The membrane should possess certain characteristics, such as

- Sufficient wet strength and water permeability
- Should be biocompatible
- Rigid and non-swelling
- Should be sufficient thick to withstand the pressure within the device.

Any polymer that is permeable to water but impermeable to solute can be used as a coating material in osmotic devices. Some of the polymers that can be used for above purpose are included in table 1[24, 25, 26].

Coating solvent

Solvents suitable for making polymeric solution that is used for manufacturing the wall of the

osmotic device include inert inorganic and organic solvents that do not adversely harm the core, wall and other materials. The typical solvents used are listed in table 1. The mixtures of solvents such as acetone-methanol (80:20), acetone-ethanol (80:20), acetone-water (90:10), methylene chloride-methanol (79:21), methylene chloride-methanol-water (75:22:3) etc. can be used [27].

Plasticizers[22]

Plasticizers lower the temperature of the second order phase transition of the wall or the elastic modulus of the wall and also increase the workability, flexibility and permeability of the fluids.

Generally from 0.001 to 50 parts of a plasticizer or a mixture of plasticizers are incorporated in to 100 parts of wall forming materials.

Suitable polymers should have a high degree of solvent power for the materials, compatible with the materials over both the processing and the temperature range, exhibit permanence as seen by their strong tendency to remain in the plasticized wall, impart flexibility to the materials and should be non-toxic. Examples of plasticizers are included in table 1.

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. These pore forming

agents cause the formation of microporous membrane. The microporous may be formed in situ by a pore former by its leaching during the operation of the system. The pore-formers can be inorganic or organic and solid or liquid in nature (table 1).

Pores may also be formed in the wall by the volatilization of components in a polymer solution or by chemical reactions in a

polymer solution which evolves gases prior to application or during application of solution to the core mass resulting in the creation of polymer foams serving as the porous wall.

The pore-formers should be non-toxic, and on their removal, channels should be formed. The channels become a transport path for fluid[27].

Table 1: Basic components of OCDDS

Components	Examples
Osmotic Agents	Water-soluble salts of inorganic acids Magnesium chloride or sulfate; lithium, sodium, or potassium chloride; sodium or potassium hydrogen phosphate Water-soluble salts of organic acids Sodium and potassium acetate, magnesium succinate, sodium benzoate, sodium citrate, sodium ascorbate Carbohydrates Mannose, sucrose, maltose, lactose Water-soluble amino acids and organic polymeric osmogens Sodium carboxymethyl cellulose, Hydroxypropylmethyl cellulose, Hydroxyethylmethylcellulose, Methylcellulose, Polyethylene oxide, Polyvinyl pyrrolidone etc.
Hydrophilic and Hydrophobic Polymers	Hydrophilic polymers Hydroxyl ethylcellulose, carboxy methylcellulose, hydroxyl propyl methylcellulose, high molecular weight poly(vinyl pyrrolidone) Hydrophobic polymers Ethyl cellulose and wax materials
Flux Regulating agents	Hydrophilic substances Polyethethylene glycols (300 to 6000 Da), polyhydric alcohols, polyalkylene glycols Hydrophobic materials Phthalates substituted with an alkyl or alkoxy (e.g., diethyl phthalate or dimethoxy ethylphthalate)
Wicking agent	Colloidal silicon dioxide, kaolin, titanium dioxide, alumina, niacinamide, sodium lauryl sulphate (SLS), poly (vinyl pyrrolidone), m-pyrol, bentonite, magnesium aluminium silicate, polyester and polyethylene
Semipermeable Polymers	Cellulose acetate, cellulose diacetate, cellulose triacetate, cellulose propionate, cellulose acetate butyrate, ethyl cellulose and eudragits
Coating solvent	Methylene chloride, acetone, methanol, ethanol, isopropyl alcohol, butyl alcohol, ethyl acetate, cyclohexane, carbon tetrachloride, water
Plasticizers	Dialkyl phthalates and other phthalates, trioctyl phosphates and other phosphates, alkyl adipates, triethyl citrate and other citrates, acetates, propionates, glycolates, glycerolates, myristates, benzoates, sulphonamides and halogenated phenyls
Pore forming agents	Alkaline metal salts such as sodium chloride, sodium bromide, potassium chloride, potassium sulphate, potassium sulphate, potassium phosphate etc., Alkaline earth metals such as calcium chloride, and calcium nitrate, Carbohydrates such as sucrose, glucose, fructose, mannose, lactose, sorbitol, mannitol and diols Polyols such as poly hydric alcohols and polyvinyl pyrrolidone

Factors influencing the design of osmotic controlled drug delivery systems

Drug Solubility

For the osmotic system, solubility of drug is one of the most important parameters affecting drug release kinetics from osmotic pumps. The kinetics of osmotic drug release is directly related to the drug solubility within the drug core. Assuming a tablet core of pure drug, the fraction of core released with zero-order kinetics is given by equation[28].

$$F(z) = 1 - S/\rho \quad (1)$$

Where, $F(z)$ is the fraction released by zero-order kinetics, S is the drug's solubility (g/cm^3), and ρ is the density (g/cm^3) of the core tablet. Drugs with a density of unity and the solubility of $\leq 0.05 \text{ g}/\text{cm}^3$ would be released with $\geq 95\%$ zero-order kinetics, according to Eq. (1).

At the same time, highly water-soluble drugs would demonstrate a high release rate that would be zero-order for a small percentage of the initial drug load. Thus, the intrinsic water solubility of many drugs might prohibit them from incorporation into an osmotic pump[29].

Candidate drugs for osmotic delivery have water solubility in the range 50–300 mg/ml. Some of the approaches that have been used to modulate drug solubility within the core include (1) co-compression of the drug with excipients, which modulate the drug's solubility within the core[30-36]; (2) use of effervescent mixtures to speed up the release of poorly soluble drug from the orifice[37]; (3)

use of various cyclodextrin derivatives to solubilize poorly water soluble drug[38-40]; (4) use of alternative salt form that has optimum water solubility[41]; (5) use of encapsulated excipients[42]; (6) use of lyotropic crystals[43,44]; (7) use of wicking agents.[45,46].

Delivery orifice

Majority of osmotic delivery systems contain at least one delivery orifice (preformed or formed in situ) in the membrane for drug release.

Size of delivery orifice must be optimized to control the drug release from osmotic system. The size of the delivery orifice must be smaller than a maximum size S_{max} to minimize drug delivery by diffusion through the orifice. Furthermore, the area must be sufficiently large, above a minimum size S_{min} , to minimize hydrostatic pressure buildup in the system. Otherwise, the hydrostatic pressure can destroy the membrane and affect the zero-order delivery rate. Therefore, the cross-sectional area of the orifice should be maintained between the minimum and maximum values[47, 48].

Methods to create a delivery orifice in the osmotic tablet coating are:

(1) Laser drill:

This technology is well established for producing sub-millimeter size hole in tablets. Normally, CO_2 laser beam (with output wavelength of 10.6μ) is used for drilling purpose. It offers excellent reliability characteristics at low costs[49, 50].

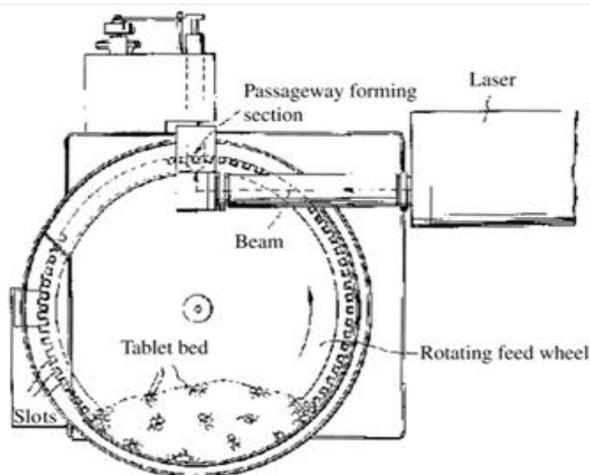
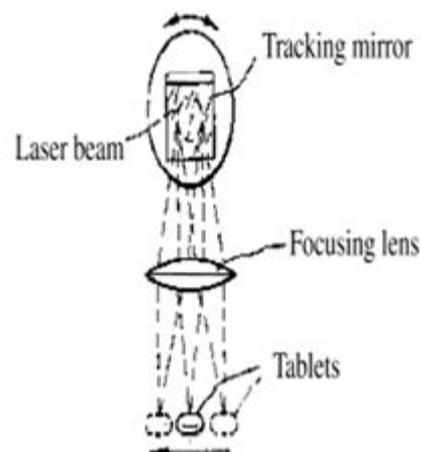


Fig. 2: Laser drilling process[49]



In simple words, the tablets in which holes are to be formed are charged in the hopper. The tablets drop by gravity into the slots of the rotating feed wheel and are carried at a predetermined velocity to the passageway forming station. At the passageway forming station, each tablet is tracked by an optical tracking system.

(2) Indentation that is not covered during the coating process[51]:

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.

(3) Use of leachable substances in the semipermeable coating:

Incorporation of water-soluble additives in the membrane wall is the most widely reported method for the formation of pores in CPOP take place. These water-soluble additives dissolve on coming in contact with water, leaving behind pores in the membrane through which drug release takes place[52].

(4) Systems with passageway formed in situ:

The system consists of a tablet core of the drug along with water-swallowable polymer and osmotic agents, which is surrounded by a rate-controlling membrane. In contact with the aqueous environment, water is imbibed osmotically at a controlled rate and water swallowable polymer expands as the osmotic agents dissolves and increases the osmotic pressure inside the tablet. This results in a rate-controlled slight expansion of the partially hydrated core. The expansion of core causes a small opening to form at the edge of the tablet (weakest point in the membrane) from where the formulation is released[53].

Osmotic pressure

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

The release rate of a drug from an osmotic system is directly proportional to the osmotic pressure of the core proportional to the osmotic pressure of the core. The simplest and most predictable way to achieve a constant osmotic pressure is to maintain a saturated solution of osmotic agent in the compartment. If a saturated solution of the drug does not possess sufficient osmotic pressure, an additional osmotic agent must be added to the core formulation. The addition of carbonate or bicarbonate salt to the drug chamber offers an advantage since the effervescent action prevents the precipitated drug from blocking the delivery orifice in the tablet[54].

Polymeric osmagents are mainly used in the fabrication of PPOPs and other modified devices for controlled release of drugs with poor

water solubility. These are swellable, hydrophilic polymers that interact with the aqueous fluids and swell or expand to an equilibrium state.

Table 2: Osmotic pressures of saturated solution of commonly used osmogents

Compound or 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 Sulfate	39
Mannitol	38
Sodium Phosphate Tribasic.12H ₂ O	36
Sodium Phosphate Dibasic.7H ₂ O	31
Sodium Phosphate Dibasic.12H ₂ O	31
Sodium Phosphate Dibasic Anhydrous	29
Sodium Phosphate Monobasic.H ₂ O	28

Semi permeable membrane [28,41]

Some of the membrane variables that are important in the design of oral osmotic system are:

Type and nature of polymer

Any polymer permeable to water but impermeable to solute can be selected. Some of the polymers that can be used for above purpose included in table 1.

Membrane thickness

Thickness of the membrane has a marked effect on the drug release from osmotic system, which is inversely proportional to each other.

Type and amount of plasticizer

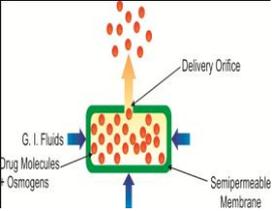
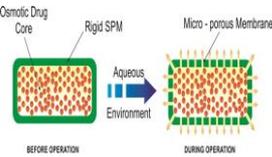
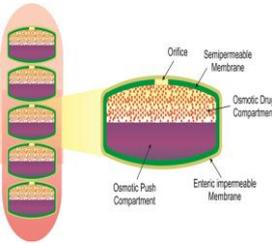
In pharmaceutical coatings, plasticizers or low molecular weight diluents are added to modify the physical properties and improve film-forming characteristics of polymers. Plasticizers can change

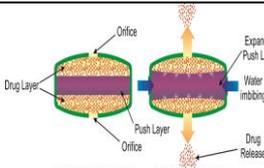
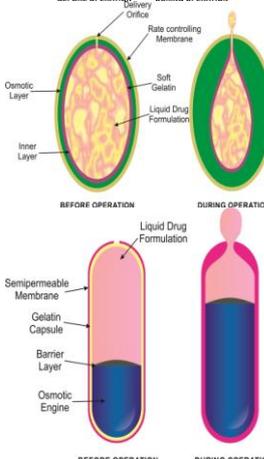
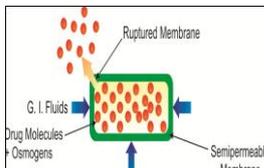
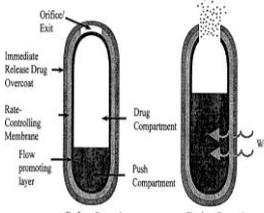
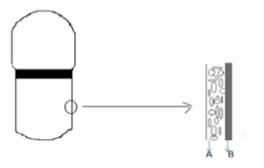
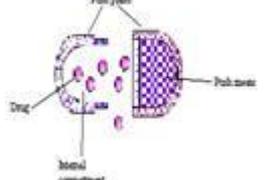
viscoelastic behavior of polymers significantly. In particular, plasticizers can turn a hard and brittle polymer into a softer, more pliable material, and possibly make it more resistant to mechanical stress. These changes also affect the permeability of polymer films.

Osmotic Pumps in Drug Delivery

Oral osmotic drug delivery systems are principally classified as follows (table 3).

Table 3: Classification of Osmotic drug delivery systems

Type of Osmotic Pump	Composition	Mechanism of Action	Advantages	Figures
Single Chamber Osmotic Pumps				
Elementary osmotic pump (EOP) [55,56]	osmotic core (containing drug with or without an osmagent) coated with a semipermeable membrane (SPM) and a small orifice is created in the membrane	Imbibes water through the SPM because of the osmotic pressure gradient and forms a saturated solution inside the device. This increases the hydrostatic pressure inside the tablet and forces the saturated drug solution through the orifice present in the membrane.	Suitable for delivery of drugs having moderate water solubility	
Osmotic Pump with Non-Expanding Second Chamber [57]	Multi-chamber devices comprise of systems containing a non-expanding second chamber.	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	Relatively insoluble drugs can also be delivered.	
Multiple Chamber Osmotic Pumps				
Push-pull osmotic pump (PPOP) [58, 59]	Two compartments: Upper compartment (drug compartment) contains the drug along with osmotically active agents. Lower compartment (push compartment) contains the polymeric osmotic agents.	When the dosage form comes in contact with the aqueous environment, both compartments imbibe water simultaneously. Because the lower compartment is devoid of any orifice, it expands and pushes the diaphragm into the upper drug chamber, thereby delivering the drug via the delivery orifice.	Deliver both highly water-soluble (oxybutynin hydrochloride) and practically water-insoluble (nifedipine, glipizide) drugs.	
Modified Osmotic Pumps				
Controlled porosity osmotic pumps (CPOP) [60, 61,62]	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.	After coming in contact with water, water soluble additives present in the coating dissolves and it results in an in situ formation of a microporous membrane as shown in figure. The release of drug takes place through this microporous channels as shown in figure.	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.	
Multiparticulate Delayed-Release System [63, 64]	Pellets containing drug with or without osmotic agent are coated with an SPM.	The osmotic pressure gradient induces a water influx, resulting in a rapid expansion of the membrane, leading to the formation of pores. The osmotic ingredient and the drug are released through these pores		
Monolithic Osmotic tablet Systems (MOTS)[65]	A simple dispersion of a water-soluble agent is made in a polymer matrix.	Water imbibitions by the active agent takes place that ruptures the polymer matrix capsule surrounding the agent, thus liberating it to the outside environment.	MOTS for a water-insoluble drug was developed using gum arabic as the osmotic, suspending, and expanding agent.	
OROS-CT [66]	System can be a single osmotic unit or it may contain as many as 5-6 push-pull units enclosed within a hard gelatin capsule.	Immediately after ingestion, hard gelatin capsule shell dissolves. Enteric coating on the system prevents entry of fluid from stomach to the system and it dissolves after entering into intestine. The drug is delivered out of the orifice at a rate controlled by the rate of water transport across the membrane.	Once- or twice-a-day formulation for targeted delivery of drugs to the colon	

<p>Sandwiched osmotic tablet (SOTS) [67]</p>	<p>Tablet core consisting of a middle push layer and two attached drug layers is coated with a SPM.</p>	<p>After coming in contact with the aqueous environment, the middle push layer containing swelling agent swells and the drug is released from the delivery orifices.</p>	<p>System delivers drug from two opposite orifices, rather than from the single orifice of the PPOP</p>	
<p>Liquid OROS controlled release system (L-OROS) [68,69]</p>	<p>Two types: <i>L-OROS Soft cap</i> and <i>L-OROS hard cap</i>. In Soft cap, Liquid drug formulation is present in a soft gelatin capsule, which is surrounded with the barrier layer, the osmotic layer, and the release rate-controlling membrane. In hard cap, it consists of a liquid drug layer and an osmotic engine, all encased in a hard gelatin capsule and coated with SPM.</p>	<p>The expansion of the osmotic layer results in the development of hydrostatic pressure, thereby forcing the liquid formulation to break through the 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.</p>	<p>To deliver APIs as liquid formulations and combine the benefits of extended release with high bioavailability. Suitable for controlled delivery of lipophilic APIs</p>	
<p>Osmotic bursting osmotic pump [70]</p>	<p>Similar to an EOP expect delivery orifice is absent and size may be smaller</p>	<p>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.</p>	<p>This system is useful to provide pulsated release.</p>	
<p>OROS Push-Stick Technology</p>	<p>It consists of a bilayer capsule shaped tablet.</p>	<p>Similar as PPOP tablets</p>	<p>Provides the greatest benefit for compounds with low water solubility and dosage greater than 150 mg.</p>	
<p>Asymmetric membrane capsule [71,72]</p>	<p>Capsule wall made up of water insoluble semipermeable polymer</p>	<p>Imbibition of water through the capsule wall and dissolving soluble components within it and releasing from same wall</p>	<p>High water permeability and controlled porosity</p>	
<p>Telescopic capsule for delayed release [73,74]</p>	<p>This device consists of two chambers, the first contains the drug and an exit port, and the second contains osmotic engine. Layer of wax-like material separates the two sections.</p>	<p>As fluid is imbibed the housing of the dispensing device, the osmotic engine expand and exerts pressure on the slidable connected first and second wall sections.</p>		

Evaluation of Oral Osmotic Drug Delivery Systems

Oral osmotic drug delivery systems can be evaluated for following:

Visual inspection: Visual inspection of the film for smoothness, uniformity of coating, edge coverage and luster.

Coating uniformity: The uniformity of coating among the tablets can be estimated by determining the weight, thickness and diameter of the tablet before and after the coating.

Coat weight and thickness: The coat weight and thickness can be determined from depleted devices following careful washing and

drying of the film, using standard analytical balance and screw gauge, respectively.

Orifice diameter: The mean orifice diameter of osmotic pump tablet can be determined microscopically using pre calibrated ocular micrometer.

In vitro drug release: The in vitro delivery rate of drugs from osmotic systems can be determined using diverse methodologies, including vertically reciprocating shaker, conventional USP dissolution apparatus I and II, flow-through apparatus, etc.

Effect of pH

An osmotically controlled release system delivers its contents independently of external variables. To check this, dissolution media with different pH is used.

Effect of agitation intensity

In order to study the effect of agitational intensity of the release media, release studies is carried out in dissolution apparatus at various rotational speeds.

In Vivo Evaluation

As the environment in the intestinal tract of the dog is quite similar to that of the human beings in terms of pH and motility, dogs have been widely used for in vivo delivery rate measurement of drug(s) from oral osmotic drug delivery systems and also to establish in vitro /in vivo correlation (IVIVC). In vivo evaluation can also be performed in healthy human volunteers. Various pharmacokinetic parameters (C_{max}, T_{max}, AUC and MRT) and relative bioavailability are calculated.

Marketed Products**Table 4: List of marketed products**

Trade Name	Active ingredient	Design system	Dose
Alpress LP	Prazosin	Push -Pull	2.5 - 5 mg
Acutrim	Phenylpropanolamine	Elementary pump	75 mg
Cardura XL	Doxazosin	Push -Pull	4, 8 mg
Covera HS	Verapamil	Push -Pull with time delay	180, 240 mg
Ditropan XL	Oxybutinin chloride	Push -Pull	5, 10 mg
Dynacirc CR	Isradipine	Push -Pull	5, 10 mg
Invega	Paliperidone	Push -Pull	3, 6, 9 mg
Efidac 24	Chlorpheniramine maleate	Elementary Pump	4 mg IR, 12 mg CR
Glucotrol XL	Glipizide	Push - Pull	5, 10 mg
Minipress XL	Prazocine	Elementary pump	2.5, 5 mg
Procardia XL	Nifedipine	Push - Pull	30, 60, 90 mg
Sudafed 24	Pseudoephedrine	Elementary pump	240 mg
Volmax	Sabutamol	Elementary pump	4, 8 mg
Tegretol XR	Carbamazepine		100, 200, 400 mg
Viadur	Leuprolide acetate	Implantable osmotic systems	
Chronogesic	Sufentanil	Implantable osmotic systems	
Concerta	Methylphenidate	Implantable osmotic systems	18, 27, 36, and 54 mg

CONCLUSION

Osmotic pumps have come a long way in the field of drug delivery, starting from complex systems developed for research purposes to the osmotic pumps used for humans. Osmotic drug delivery systems are based on utilization of osmosis as driving force for drug delivery. Since its origin 25 years ago, osmotic drug delivery systems have come a long way and are still used as research tool to study the delivery of drugs with different physicochemical and pharmacokinetic properties. The release of drug(s) from these types of systems is affected by various formulation factors such as solubility and osmotic pressure of the core component(s), membrane characteristics, and size of the delivery orifice. By modulating these formulation factors, it is possible to use these systems to deliver variety of drugs of at a pre-programmed rate. The products available in the market, patents done till date and effectiveness obtained for osmotic products are indicative of success of this drug delivery in future too.

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