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Oral Osmotic Drug Delivery System-An Overview



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ABSTRACT

The oral route is the most common and most preferable route of drug administration. For the treatment of chronic diseases, repeated dose administration is required, the osmotic drug delivery system serves as a tool for control release of drugs in this condition and avoids the repeated administration. The conventional drug delivery systems have little control over their drug release and almost no control over the effective concentration at the target site. This kind of administration may result in constantly changing, unpredictable plasma concentrations. By osmosis, process drugs can be delivered in a controlled pattern over a long period. Osmotic devices are the most promising strategy based systems for controlled drug delivery. This system could be employed as oral drug delivery systems and they are the most reliable controlled drug delivery systems. Osmotic drug delivery systems release the drug with zero-order kinetics which does not depend on the initial concentration and the physiological factors of GIT. This review gives an idea of the osmotic drug delivery system and its evaluation.



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INTRODUCTION

Novel drug delivery systems (NDDS) are the main field of pharmaceutical research and development. Because the capital required is low, many conventional drug delivery systems have been designed to regulate the release of a drug over an extended period^[1]. Numerous designs are available to control or modulate the release of drug from a dosage form. Conventional matrix or reservoir type formulations reveals the problem of bioavailability variations due to alterations in gastric pH. Additionally, the release of drugs from these systems is affected by the hydrodynamic conditions of the body^[2]. The drug absorption from conventional formulations may depend on the factors such as physicochemical properties of the drug, presence of Excipients, physiological factors such as presence or absence of food, pH of the gastrointestinal tract (GI) and so on^[3]. Osmotically controlled drug delivery systems (OCDDS) is one of the most promising drug delivery technology that uses osmotic pressure as a driving force for controlled delivery of active ingredients. 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 delivering orifice used in osmotic systems, so a high degree of *in-vitro/in-vivo* correlation is achieved^[4,5]. Osmosis is defined as the movement of a solvent through a selectively permeable membrane into an area of higher solute concentration, the result of which will be an equalizing of solute concentration on either side of the membrane. Osmotic pressure is the pressure which, if applied to the more concentrated solution, would prevent the transport of water across the semi-permeable membrane. The Osmotic Controlled Release Preparation is a novel drug delivery system with eternally drug delivery rate as characteristic and controlled with the osmotic pressure difference between inside and outside of the semipermeable membrane as drug delivery power^[6].

Advantages of Osmotic Drug Delivery System^[7]

- 1) The osmotic systems release rates are higher than with conventional diffusion-based delivery systems.
- 2) The true zero-order delivery rate can be archived by osmotic systems.
- 3) Drug release is minimally affected by gastric pH and hydrodynamic conditions of the body in osmotic systems.

- 4) In osmotic systems, the release rate is highly predictable and it can be programmed by modulating the release control parameters.
- 5) In osmotic systems, the high degree *in-vivo/in-vitro* correlation can be obtained.
- 6) In osmotic systems, the drug release is minimally affected by the presence of food.

Disadvantages of Osmotic Drug Delivery System^[8]

- 1) The osmotic pump tablets should not be crushed or chewed as it can lead to loss of 'slow release' characteristics.
- 2) The release rate of the drug can be altered by food and gastric transit time.
- 3) The method of preparation is very costly.
- 4) If the coating process is not well controlled they have a chance of dose dumping.

Basic Components of the osmotic system

- Drug
- Osmotic agent
- Semipermeable membrane
- Wicking agent
- Pore-forming agent
- Coating agent



Drug^[9]

Drugs that have a low biological half-life (2-6 hrs) and which are used for prolonged treatment are the ideal candidate for osmotic systems. Various drug candidates such as Diltiazem hydrochloride, Carbamazepine, Metoprolol, Oxprenolol, Nifedipine, Glipizide, etc. are formulated as osmotic delivery.

Drug having following characteristics are suitable for formulation.

1. The drug should have a short half-life.
2. Prolonged-release of the drug should be desired.
3. The drug should be potent.
4. The solubility of the drug should not be very high or very low.

Osmotic agent^[10]

Osmotic agents are used to maintaining the concentration gradient across the membrane. They generate a driving force for the uptake of water and assist in maintaining the drug uniformity in a hydrating formulation. Osmotic components are usually ionic compounds consisting of either hydrophilic polymers or inorganic salts. The different type of osmogens can be used for such systems are categorized in Table 1.

Semipermeable membrane^[11]

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 must possess certain characteristics, such as

- Sufficient wet strength and water permeability.
- Should be biocompatible.
- Should be sufficiently thick to withstand the pressure within the device.

Any polymer that can be permeable to water but impermeable to solute can be used as a coating material in osmotic devices. Some polymers that can be used for the above purpose are included in table 1.

Wicking agent^[12]

Wicking agent is defined as the material which ability to draw water into the porous network of a delivery device. A wicking agent is either swellable or non-swellable nature. The function of a wicking agent is to carry water to the surfaces inside the core of the tablet, thereby creating a channel or a network of increased surface area.

Pore forming agents^[13]

Pore-forming agents are particularly used in the pumps developed for poorly water-soluble drugs and in the development of controlled porosity or multiparticulate osmotic pumps. Pore-forming agents cause the formation of a microporous membrane. These microporous may be formed in situ by a pore former by its leaching during the operation of the system. The pore-formers can be solid or liquid and inorganic or organic.

The pore-formers should be non-toxic, on their removal channels should be formed. The channels become a transport path for the fluid. (table 1)

Coating agent^[14]

Solvents are suitable for making a 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 such as methylene chloride, acetone, methanol, ethanol, isopropyl alcohol, butyl alcohol, ethyl acetate, cyclohexane, carbon tetrachloride, water, etc. The mixtures of solvents such as acetone-methanol (80:20), acetone-ethanol (80:20), acetone-water (90:10), methylene chloride-methanol (79:21), methylene chloride-methanol-water (75:22:3), etc, can be used.

Ideal properties of the solvent system.

- (1) It shall easily and completely dissolve the polymer.
- (2) It shall easily disperse other coating components into the solvent system.
- (3) It must be odorless, colorless, tasteless, inexpensive, non-toxic and non-irritant.
- (4) It must have a rapid drying rate.

Table No. 1: Basic components of OCDDS

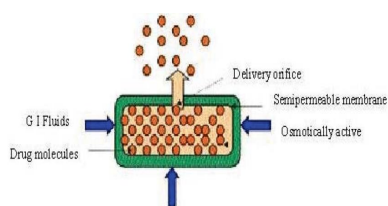
Components	Examples
Osmotic agents	<p>Water-soluble salts of inorganic acids Magnesium chloride or sulfate; lithium, sodium, or potassium chloride; sodium or potassium hydrogen phosphate</p> <p>Water-soluble salts of organic acids Sodium and potassium acetate, magnesium succinate, sodium benzoate, sodium citrate, sodium ascorbate</p> <p>Carbohydrates Mannose, sucrose, maltose, lactose</p> <p>Water-soluble amino acids and organic polymeric osmogents Sodium carboxymethyl cellulose, Hydroxypropylmethylcellulose, Hydroxyethylmethylcellulose, Methylcellulose, Polyethylene oxide, Polyvinyl pyrrolidone, etc.</p>
Semipermeable Polymers	Cellulose acetate, cellulose diacetate, cellulose triacetate, cellulose propionate, cellulose acetate butyrate, ethyl cellulose.
Wicking agent	Colloidal silicon dioxide, kaolin, titanium dioxide, alumina, niacinamide, sodium lauryl sulfate (SLS), poly (vinyl pyrrolidone), m-pyrrol, bentonite, magnesium aluminum silicate, polyester and polyethylene
Pore-forming agents	<p>Alkaline metal salts such as sodium chloride, sodium bromide, potassium chloride, potassium sulfate, potassium phosphate, etc.,</p> <p>Alkaline earth metals such as calcium chloride, and calcium nitrate,</p> <p>Carbohydrates such as sucrose, glucose, fructose, mannose, lactose, sorbitol, mannitol and diols Polyols such as polyhydric alcohols and polyvinyl pyrrolidone</p>
Coating solvent	Methylene chloride, acetone, methanol, ethanol, isopropyl alcohol, butyl alcohol, ethyl acetate, cyclohexane, carbon tetrachloride, water

CLASSIFICATION OF OSMOTIC DRUG DELIVERY SYSTEM:

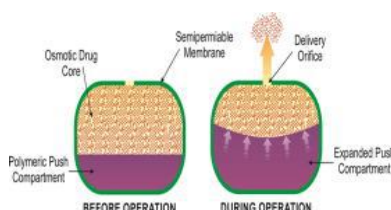
Table No. 2: Classification of osmotic drug delivery system

Type of Osmotic Pump	Composition	Mechanism of Action	Advantages
<p>Single Chamber Osmotic Pumps^[15] Elementary osmotic pump</p>	<p>The osmotic core (containing drug with or without an osmagent) coated with a semipermeable membrane (SPM) and a small orifice is created in the membrane</p>	<p>Imbibes water through the SPM because of 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</p>	<p>This is Suitable for delivery of drugs having a moderate water solubility</p>
<p>Multiple Chamber Osmotic Pumps^[16] Push-pull osmotic pump (PPOP)</p>	<p>Two compartments: Upper compartment (drug compartment) contains the drug along with osmotically active agents. Lower compartment (push compartment) contains polymeric osmotic agents</p>	<p>When the dosage form comes in contact with an 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.</p>	<p>It delivers both highly water-soluble (oxybutynin hydrochloride) and practically water-insoluble (nifedipine, glipizide) drugs</p>
<p>Modified Osmotic Pumps^[17] Controlled porosity osmotic pumps (CPOP)</p>	<p>CPOPs are similar to EOP and the difference is being that the delivery orifice from which the drug release takes place is formed by incorporation of a water-soluble additive in the coating</p>	<p>After coming in contact with the water, water-soluble additives present in the coating dissolves and it results in an <i>in-situ</i> formation of a microporous membrane as shown in the figure. The release of the drug takes place through these microporous channels as shown in the figure.</p>	<p>This type is suitable for the delivery of drugs having intermediate water solubility and extremes of water solubility by some modifications.</p>

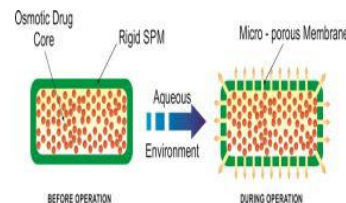
Elementary osmotic pump



Push-pull osmotic pump

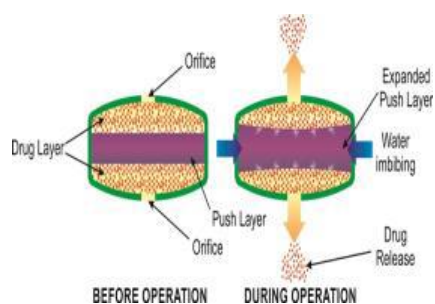


Controlled porosity osmotic pump

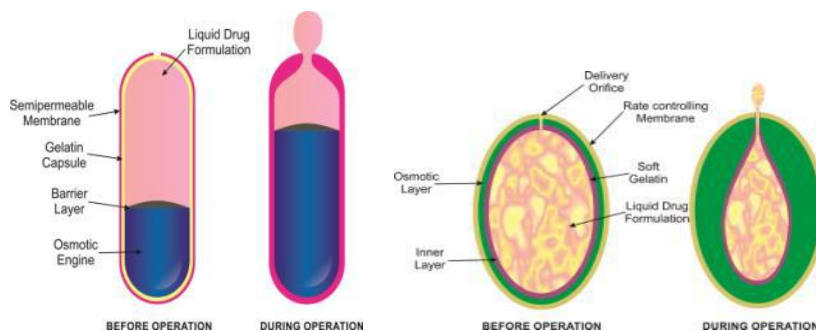


Type of Osmotic Pump	Composition	Mechanism of Action	Advantages
<p>Sandwiched osmotic tablet^[18]</p>	<p>Tablet core consisting of a middle push layer and two attached drug layers is coated with a SPM.</p>	<p>After coming in contact with the aqueous environment and the middle push layer containing swelling agent swells and the drug is released from the delivery orifices.</p>	<p>The system delivers the drug from two opposite orifices, rather than the single orifice of the PPOP</p>
<p>Liquid OROS controlled release system^[19] (L-OROS)</p>	<p>Two types: L-OROS Soft cap and L-OROS hard cap. In Soft cap, Liquid drug formulation is present in a soft gelatin capsule and which is surrounded by 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 and 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 thereby 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>

Sandwiched osmotic tablet



Liquid OROS controlled release system

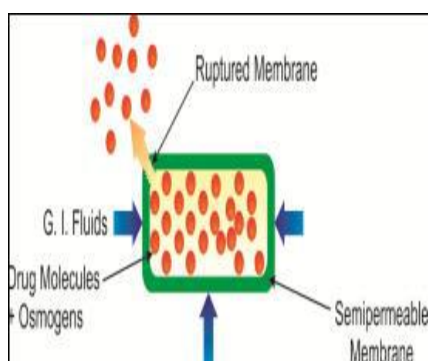


L-OROS Hard cap

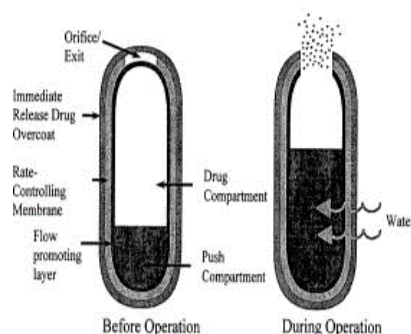
L-OROS Soft cap

Type of Osmotic Pump	Composition	Mechanism of Action	Advantages
Osmotic Pump with Non-Expanding Second Chamber^[20]	Multi-chamber devices comprise of systems containing a non-expanding second chamber	The purpose of the second chamber is either dilution of drug solution leaving the device (useful in handling drugs with a high incidence of GI irritation) or simultaneous delivery of two drugs	Relatively insoluble drugs can also be delivered.
Osmotic bursting osmotic pump^[21]	Similar to an EOP. 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 ruptures and the contents are released to the environment.	This type of system is useful to provide pulsated release.
OROS Push-Stick Technology^[22]	It consists of a bilayer capsule-shaped tablet	Similar to PPOP tablets	Provides the greatest benefit for compounds with low water solubility and dosage greater than 150 mg
Telescopic capsule for delayed release^[23]	This device consists of two chambers, first contain the drug and an exit port, and the second contains an osmotic engine. The layer of wax-like material separates the two sections	As the fluid is imbibed housing of the dispensing device, the osmotic engine expands and exerts pressure on the slidable connected first and second wall sections.	

Osmotic bursting osmotic pump



OROS Push-Stick Technology



KEY PARAMETERS FOR DESIGNING OF OSMOTIC DRUG DELIVERY SYSTEMS:

OSMOTIC PRESSURE

Osmotic pressure is a solution depending on several discrete entities of solute presents in the solution. The release rate of a drug from the osmotic system is directly proportional to the osmotic pressure. For controlling the drug release from these systems, it is important to optimize the osmotic pressure gradient between the inside compartment and external environment. It is possible to maintain a constant osmotic pressure by maintaining the solution of the osmotic agent in the core compartment. If a drug does not possess sufficient osmotic pressure then an osmotically active agent can be added to the formulation.

The Polymeric cosmogenic are mainly used in the fabrication of PPOPs and other modification devices for the controlled release of drug with poor water solubility. There are swellable, hydrophilic polymers that interact with the aqueous fluids and swell or expand to an equilibrium state. These polymers can remain a significant portion of the imbibed water within the polymer stricter^[24].

DELIVERY ORIFICE^[25]

To achieve an optimal zero order delivery profile, the cross-sectional area of the orifice should be smaller than a maximum size to minimize drug delivery by diffusion through the orifice. Furthermore, the area should be sufficiently large, above a minimum size to minimize hydrostatic pressure build up in the system. The typical orifice size in the osmotic pumps ranges from 600 μ m 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 making sub-millimeter size hole in tablets. Normally, a CO₂ laser beam (with an output wavelength of 10.6μ) is used for drilling purpose, which offers excellent reliability characteristics at low costs.
- The indentation that is not covered during the coating process: Indentation is made in core tablets by using modified punches having a needle on the upper punch. This is not covered during the coating process which acts as a path for drug release in the osmotic system.

Type and nature of polymer^[26]

The membrane in the osmotic system is semi-permeable so any polymer that is permeable to water but impermeable to solute can be selected. Some of the polymers that can be used for the above purpose include cellulose esters such as cellulose acetate, cellulose diacetate, cellulose triacetate, cellulose acetate butyrate, cellulose propionate, etc. Cellulose ethers like ethyl cellulose and eudragits.



Use of wicking agents^[27]

Incorporation of the wicking agents in osmotic formulations has been reported as an approach for the poorly water-soluble drugs. The agent is dispersed throughout the composition that increases the contact surface area of drug with a contact of the aqueous fluids e.g. colloidal silicon dioxide, sodium lauryl sulfate, etc. Hence the drug is released predominantly in a soluble form through the delivery orifice in the membrane.

Effect of type of plasticizer on the release profile^[28]

Plasticizers can change the viscoelastic behavior of the 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 and these changes also affect the permeability of polymer films. The water permeability of CA films was found to decrease with increasing plasticizer concentration to a minimum and then increases with a higher concentration of plasticizer.

Drug solubility^[29]

The Absorption of poorly soluble drugs is often dissolution rate limited. Such drug does not require any further control over their dissolution rate, during the Pre-formulation phase it is necessary to determine the drug solubility not only in water but also at various pH values. The aqueous and pH-dependent solubility is of importance for drug release. The hydro solubility of the drug plays an important role in the drug release mechanism, soluble drugs are generally released by diffusion mechanism while insoluble drugs are released by erosion mechanism.

Evaluation

1) Pre Compression Parameters

A. Bulk density (D_b):^[30]

It is the ratio of powder to the bulk volume. The bulk density depends on the particle size distribution, shape, and cohesiveness of particles. Accurately weighed quantity of powder was carefully poured into the graduated measuring cylinder through large funnel and volume was measured which is called initial bulk volume. The Bulk density is expressed in gm/cc and is given by,

$$D_b = M / V_o$$

Where, D_b = Bulk density (gm/cc)

M is the mass of powder (g)

V_o is the bulk volume of powder (cc)

B. Tapped density (D_t):^[31]

The measuring cylinder containing a known mass of granules blend and the cylinder was then tapped 100 times from a constant height and tapped volume was read. It is expressed in gm/cc and is given by,

$$D_t = M / V_t$$

Where, D_t = Tapped density (gm/cc)

M is the mass of powder (g)

V_t is the tapped volume of powder (cc)

C. Compressibility index:^[32]

Compressibility index determines the flow property characteristics of granules developed by Carr.

The compressibility of the powder was determined by Carr's compressibility index.

$$\text{Carr's index (\%)} = \frac{b-(v/b)}{b} \times 100$$

Sr. No.	Carr's Index	Flow Properties
1	5-15	Excellent
2	12-15	Good
3	18-21	Fair to Passable
4	23-30	Poor
5	33-38	Very Poor
6	>40	Very Very Poor

D. Hausner ratio:^[33]

Hausner's ratio is used for the determination of flow properties of granules.

$$\text{Hausner's ratio} = \frac{\text{tapped density}}{\text{bulk density}}$$

Values of Hausner ratio; < 1.25: good flow

>1.25: poor flow

If the Hausner ratio is between 1.25-1.5, flow can be improved by the addition of glidants.

E. Angle of repose (θ):^[34]

It is defined as the maximum angle possible between the surface of the pile of the powder and the horizontal plane. Fixed funnel method was used. A funnel was fixed with its tip at a given height (h), above a flat horizontal surface on which a graph paper was placed. The

powder was carefully poured through a funnel till the apex of the conical pile just touches the tip of the funnel. The angle of repose was then calculated using the formula,

$$\tan\theta = h/r$$

$$\theta = \tan^{-1}(h/r)$$

where, θ = angle of repose,

h = height of pile,

r = radius of the base of the pile

2. Post compression parameters:

A. Thickness:^[35]

The thickness of individual tablets is measured by using Vernier caliper which gives the accurate measurement of thickness. It provides information on the variation of thickness between osmotic tablets. The unit for thickness measurement is mm. The limit for the thickness deviation of each tablet is $\pm 5\%$.

B. Hardness:^[36]

The tablet hardness can be determined by Monsanto hardness tester. The tablet was held between a fixed and moving jaw. The scale was adjusted to zero loads was gradually increased until the tablet fractured. The value of the load at that point gives a measure of the hardness of the tablet. Hardness was expressed in Kg/cm^2 .

C. Friability(F):^[37]

Tablet strength was tested by Friabilator. Tablets were initially weighed (W_0) tablets were allowed for 100 revolutions, The tablets are taken out and were dusted and reweighed (W). The percentage of weight loss was calculated by rewriting the tablets. The % friability was then calculated by using the formula,

$$\% \text{ Friability} = F = \left(1 - \frac{W}{W_0}\right) \times 100$$

D. Weight variation test:^[38]

The weight of the tablet is measured to ensure that a tablet contains the proper amount of drug. The USP weight variation test was done by weighing 20 tablets individually calculating the average weight and comparing the individual weights to the average. The tablet meets the USP test if not more than 2 tablets are outside the percentage limits and if no tablets differ by more than 2 times the percentage limit. USP official limits of percentage deviation of the tablet are presented in the following table,

The average weight of tablets (mg)	Maximum percentage difference allowed
130 or less	±10
130 to 324	±7.5
More than 324	±5

E. Disintegration test:

In disintegration test apparatus, the disintegration time of tablets is measured by placing tablets in each tube, and the basket rack assembly is positioned in a 1-liter beaker of the water or simulated gastric fluid or simulated intestinal fluid at $37^{\circ}\text{C} \pm 2^{\circ}\text{C}$ such that the tablet remains 2.5 cm from the bottom of the beaker. A standard motor moves basket up and down through a distance of 5 to 6 cm at a frequency of 28 to 32 cpm (cycles per minute). USP disintegration test will be passed if all the tablets disintegrate and the particles are passed through the #10 mesh screen within the specified time.

F. *in-vitro* dissolution studies:^[39]

in-vitro dissolution study is performed by using a suitable USP Type Apparatus. The tablet is kept in 900 ml of dissolution fluid suitable buffer of suitable pH or simulated gastric fluid with a stirrer rotating at a specified r.p.m and maintaining the temperature at $37 \pm 0.5^{\circ}\text{C}$ of dissolution media. 5 ml of the samples withdrawn at different time intervals were replaced with fresh medium and analyzed in UV-Visible spectrophotometer for estimation of the absorbance taking a suitable blank solution. Finally, the drug release rate is calculated using a suitable equation.

MARKETED PRODUCTS:

Table No. 3: Marketed products of Osmotic drug delivery system

Sr. No.	Brand name	Active pharmaceutical ingredient	Developer/Marketer	Ref. No.
01	AlpressLP	Prazosin	Alza/Pfizer	40
02	Glucotrol XL	Glipizide	Alza/Pfizer	41
03	ProcardiaXL	Nifedipine	Alza/Pfizer	42
04	Tiamate	Diltiazem	Merck/Aventis	43
05	CarduraXL	Doxazosin	Alza/Pfizer	44
06	Volmax	Albuterol	Alza/Muro	45
07	DitropanXL	Oxybutinin chloride	Alza/UCB Pharma	46
08	Dynacire CR	Isradipine	Alza/Novartis	47
09	Efidac24	Pseudoephedrine	Alza/Novartis	48
10	Acutrim	Phenylpropanolamin	Alza/Heritage	46

PATENTS ON OSMOTIC DRUG DELIVERY SYSTEM:

Table No. 4: Patents on osmotic drug delivery system

Sr. No.	Patent no.	Title	Publication date	Inventors	Refno.
01	US3977404	An osmotic device having the microporous reservoir	Aug.31,1976	Felix Theeuwes	49
02	US4285987	The osmotic system for dispensing drugs	Aug.25,1981	Atul.D.Ayer, F.Theeuwes	50
03	EP0169105	Controlled porosity osmotic pump	Jan.22,1986	Gaylen M.Zentner, Gerald S.Rork, Kenneth J.Himmelstein	51
04	US4946686	Solubility modulated drug delivery system	Aug.7,1990	Gregory A. Mcclelland, Gaylen M.Zentner	52
05	EP0309051	Controlled porosity osmotic pump	Mar.11,1992	John L.Haslam, Gerald S.Rork	53
06	WO1994001093	Controlled porosity osmotic enalapril pump	Jan.20,1994	John L.Haslam, Gerald S.Rork	54
07	US5672167	Controlled release osmotic pump	Sept.30,1997	Amulya L. Athayde, Rolf A.Faste, C.Russell Horres Jr, Thomas P.Low	55
08	WO2001032149	Osmotic controlled-release drug delivery device	May 10, 2001	Laura A Debusi, Stephen B Ruddy, David E Storey	56
09	US8109923	Osmotic pump with remotely controlled pressure generation	Feb.7,2012	LE Hood, MY Ishikawa, EKY Jung, R Langer, T Clarence, TLL Wood, VYH Wood	57

CONCLUSION

In osmotic delivery systems, the osmotic pressure provides the driving force for drug release. Increasing pressure inside the dosage form. water incursion causes the drug to release from the system. The major advantages include the precise control of zero-order or another patterned release over an extended period consistent release rates can be achieved, irrespective of the environmental factors at the delivery site. However, a complex manufacturing process and higher cost compared with the conventional dosage forms limit their use. Although not all drugs are available for treating different diseases require such precise release rates, once-daily formulations based on osmotic principles are playing an increasingly important role in improving patient compliance. Therefore, most of the currently marketed products are based on drugs used in long-term therapies for diabetes, hypertension, and other chronic disease states. Besides oral osmotic delivery systems. once-daily formulations based on osmotic principles are playing an increasingly important role in improving patient compliance.

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