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A Review on Osmotically Controlled Oral Drug Delivery Systems

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ABSTRACT:

In the pharmaceutical research and development the novel drug delivery system (NDDS) plays remarkable performance. A milestone in oral NDDS is innovative and highly versatile drug delivery system. ODDS use the principle of osmotic pressure, as an energy source, for the delivery of drugs. Oral osmotic drug delivery systems with their versatile and their highly predictable drug release rates offer various biomedical advantages. Osmosis is one type of aristocrat phenomenon that seizes the attention for its exploitation in zero-order drug delivery systems. The drug delivered from these systems is not reliable of pH and the physiological conditions. Optimizing semipermeable membrane and the osmotic agents can modulate drug release from the system. In this article, a detailed description of various oral osmotically driven systems along with their formulation aspects, therapeutic applications and evaluation techniques are described.

KEYWORDS: Drug delivery system, Osmotic pressure, Zero- order release rate, Semipermeable membrane.

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INTRODUCTION:

The overall action of a drug molecule is dependent onits inherent therapeutic activity and the efficiency with which it is delivered to the site of action. An increasing appreciation of the latter has led to the evolution and development of novel drug delivery systems (NDDS), aimed at performance enhancement of potential drug molecules. 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 ñ 50 million and 3 ñ 4 years, respectively) as compared to new chemical entity (approximately $500 million and10 ñ 12 years, respectively) [1]. The focus on NDDS includes, design of NDDS for new drugs on one hand and on the other NDDS for established drugs augment commercial viability.

Oral route remains one of the most ënaturalí routes of drug administration and has seen remarkable accomplishments in the last couple of decades towards optimization of oral delivery of drug molecules. Oral ingestion is one of the oldest and most extensively used routes of drug administration, providing a convenient method of effectively achieving both local and systemic effects [2].

Drug Delivery describes a process whereby a therapeutic agent is administered to the body in a controlled manner. Advanced drug delivery technologies can improve a product is clinical and commercial value, differentiate a product, and serve as an effective resource to outsmart competition. Drug delivery technologies make medicine more convenient and acceptable to a patient by simplifying the dosing regimen and improving administration. Although a number of NDDS have been successfully commercialized, per oral controlled release

systems continue to hold the major market share. A significant milestone in oral NDDS is the development of the Osmotic drug delivery system, an innovative and highly versatile drug delivery system [3].

Osmotic drug delivery systems (ODDS) differ from diffusion-based systems in that; the delivery of the active agent(s) is driven by an osmotic gradient rather than the concentration of drug in the device [4]**.** Osmotic devices are most promising strategy based systems for controlled drug delivery. They are among the most reliable controlled drug delivery systems and could be employed as oral drug delivery systems or implantable devices [3]**.** Osmosis is an aristocratic biophenomenon, which is exploited for development of delivery systems with every desirable property of an ideal controlled drug delivery system. There are over 240 patented osmotic drug delivery systems [5]**.** Osmotic drug delivery systems are unique in the sense that the delivery of drug(s) is not dependent / influenced by physiological variables within the GIT, these systems are adaptable to a number of drugs, with minor modifications and the delivery of drug(s) can be predictably controlled in a useful manner. The oral osmotic pumps have certainly come a long way and a number of patents granted in the last few years makes it presence felt in the market **(Table-1)[**5,6].

Table1: List of Some Important Patents Based on Osmotic Drug Delivery

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

They are also known as GITS (gastro-intestinal therapeutic system) [1] and today, different types of osmotic pumps, of various drugs, are available in the market to meet patients' need and requirement **(Table-2)** [7,8].

Table 2 List of commercially marketed oral osmotic drug delivery Products.

Product name	Drug
Acutrim	Phenylpropranolamine
Alpress LP	Prazosin
Calan SR	Verapamil
Cardura XL	Doxazocin mesylate
Concenta	Methylphenidate
Covera HS	Verapamil
Ditrophan XL	Oxybutynin chloride
DynaCirc CR	Isradipine
Efidac 24	Pseudoephedrine
Glucotrol XL	Glipizide
Ivomec SR Bolus	Ivernectin
Minipress	Prazosin
Procardia XL	Nifedipine
Teczem	Enalapril and Diltiazem
Tiamate	Diltiazem
Volmax	Albuterol
Viadur	Leuprolide acetate

Osmotic pumps offer many advantages over other controlled drug delivery systems, i.e. they are easy to formulate and simple in operation, improve patient compliance with reduced dosing frequency and more consistent and prolonged therapeutic effect with uniform blood concentration. They are inexpensive and production scale up is easy [9].

Principle

An osmotic system releases a therapeutic agent at a predetermined, zero order delivery rate based on the principle of Osmosis, which is movement of a solvent from lower concentration of solute towards higher concentration of solute across a semi-permeable membrane [9]**.**

After administration of osmotic system, water is imbibed into the core osmotically through semi permeable membrane resulting in development of hydrostatic pressure that pumps drug containing solution or suspensions out of the core through one or more delivery ports. The delivery from the system is controlled by the water influx through semipermeable membrane. Water influx into osmotic system can be described by the following equation [10].

$$dv/dt = A\theta\Delta\pi/l \text{.....} \quad \textbf{Equation – 1}$$

where, dv/dt is water influx, A is the membrane area, Lp is mechanical permeability, б is reflection coefficient and Δπ and Δ*p* are the osmotic and hydrostatic pressure differences, respectively, between the inside and outside of the system and h is the thickness of membrane. The general expression for the solute delivery rate, dM/dt, obtained by pumping through the orifice is given by:

$$Z = \left(\frac{dm_d}{dt}\right)_z = K \frac{A}{h} \pi_t S_d \quad \text{.....Equation – 2}$$

Where, C is the concentration of compound in the Dispensedfluid. Reflection coefficient takes into account the leakage of solute through the membrane. A perfectly semipermeable membrane (SPM) is selectively permeable to water only and does not allow solute to pass through it. Thus, in case of a perfectly semipermeable membrane, □ is close to unity. As size of the delivery orifice increases, hydrostatic pressure inside the system is minimized and Δπ >>> Δ*p.* Since, osmotic pressure of the gastrointestinal fluids is negligible as compared to that of core; π can be safely substituted for Δπ. By replacing the product Lp б, in Eq. (1), by a constant K and substituting Eq. (1) in Eq. (2), the following equation is obtained:

$$Zd = K \frac{A^2}{w} \rho_m \pi_t S_d \quad \text{.....Equation – 3}$$

The best possible way to achieve a constant release from osmotic systems is through proper selection and optimization of the SPM (to maintain the first three terms on the right hand side of the equation constant) and maintaining a saturated solution of drug within the core. As long as excess solid agent is present inside the system, both □and C in Eq. (3) can be maintained at constant levels. Therefore, it is possible to obtain constant zero-order release rates from osmotic systems by maintaining the terms in Eq. (3) constant [5].

Advantages Osmotic drug delivery systems have the following advantages over other controlled release formulations **[**2, 11, and 12]

- Provides Zero-order delivery rate.
- Delayed or pulsed drug delivery is obtainable with osmotic system.
- The delivery rate is significantly greater than that attainable with diffusion based system(s) of comparable size.
- In vitro delivery rate can be accurately predicted using mathematical equations, which in turn, bears high degree of correlation with in-vivo delivery rate.
- Delivery rate is independent of pH variations in the environment, including those in the gastrointestinal tract (GIT).
- Delivery rate is independent of agitation outside, including GI motility.
- Release rate from osmotic system is highly predictable and programmable.
- Delivery of drug takes place in the solution form ready for absorption, with osmotic pump simulating as a liquid dosage form prepared in-situ.
- Delivery rate is almost independent of delivery orifice size within limits.
- Drugs with widely varying solubility can be incorporated.
- The device is relatively simple to fabricate using conventional pharmaceutical manufacturing equipment

Classification

Oral osmotic drug delivery systems are principally classified as follows [13, 14] (Fig. 1).

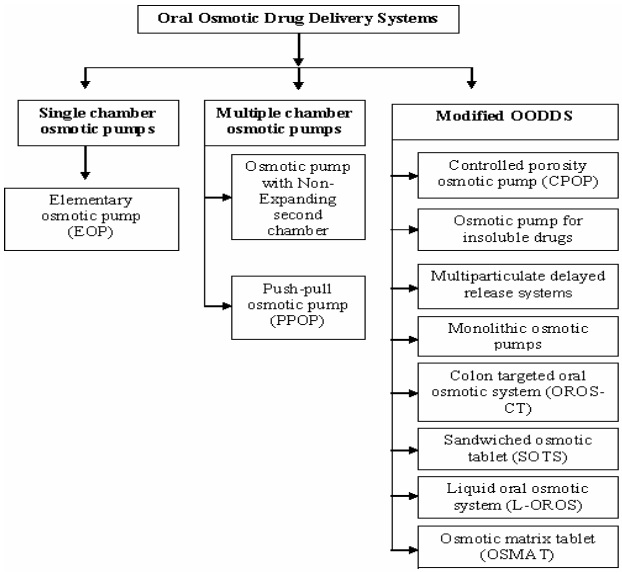

Figure 1: Classification of the Oral Osmotic Drug Delivery Systems

Elementary Osmotic Pump (EOP): Theeuwes developed elementary osmotic pump in 1975[10]. An EOP is the most basic device made up of a compressed tablet. The EOP consists of an osmotic core with the drug, surrounded by a semipermeable membrane **[**15]. The semipermeable membrane is provided with a hole for the controlled delivery of the saturated solution of the drug formed as a result of imbibition of water whose rate is determined by the fluid permeability of the membrane and the osmotic pressure of the compressed tablet when the dosage form is placed in the aqueous environment (Fig. 2). Though 60% to 80% of drug is released at a constant rate from EOP, a lag time of 30 to 60 minutes is observed in most of the cases as the system hydrates before zero-order delivery from the system begins [1]**.**

The main components of the EOP are as osmotic core which comprises a drug with good (not less than 10%) aqueous solubility with or without osmogens and osmogens which could be selected from among pharmaceutically accepted salts, sugars and organic compounds like sucrose, mannitol, etc. the osmotic pressure of soluble solutes is extremely high,

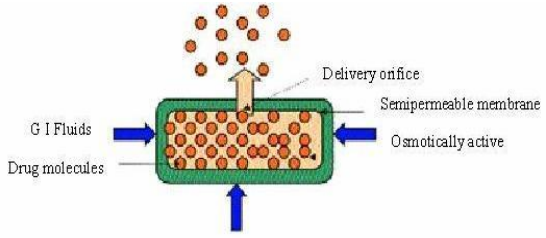

Figure 2: Elementary Osmotic Pump

as is evident from Table 3, which shows osmotic pressure of the commonly used solutes in controlled release formulations[16].

Table 3: Osmotic Pressure of Saturated Solutions of Common Pharmaceutical Solutes

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. 12 H2O	36
Sodium phosphate dibasic .7 H2O	31
Sodium phosphate dibasic. 12 H2O	31
Sodium phosphate dibasic anhydrous	29
Sodium phosphate monobasic. H2O	28

Semipermeable membrane (SPM) is another component which is made up of polymers include cellulose ethers, cellulose esters, acylated polysaccharides, nitrated polysaccharides, polymer epoxides, vinyl polymers, polystyrene derivatives, polyesters, polyamides, polyacrylates, etc.[1]**.** The semipermeable coating could be obtained by conventional film coating techniques. Fourth component is delivery orifice which is normally drilled by laser technique **[**17].

Osmotic Pump with Non-Expanding Second Chamber: These multichamber devices comprise of systems containing a non-expanding second chamber. The 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 by formulating them in this type of device [2].

Push-Pull Osmotic Pump (PPOP): It is a bilayer tablet coated with semi permeable membrane. The PPOP system consists of two compartments separated usually by an elastic diaphragm. The upper compartment contains the drug and is connected to the outside environment via a small delivery orifice **(Fig.3).**

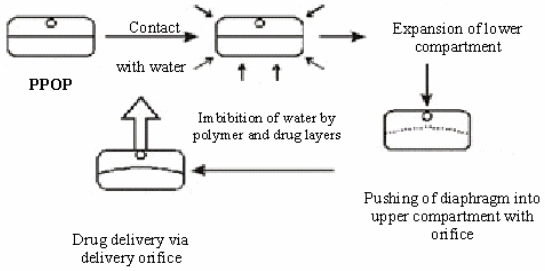

Figure 3: Mechanism of Drug Delivery from a Push-Pull Osmotic Pump (PPOP)

A swellable polymer osmotic agent is present in the lower compartment, accounting for around 20-40 per cent of the tablet. The upper layer consists of drug and the delivery orifice, and accounts for 60-80 per cent of tablet weight **[**2,18]**.** PPOP can be used to deliver drugs with extremes of water solubility. Push ñpull system is available in number of modifications such as delayed push-pull system, multiplayer push-pull system and push-stick system [14].

Controlled Porosity Osmotic Pump (CPOP): Controlled porosity osmotic pump contains water- soluble additives in the coating membrane, which after coming in contact with aqueous environment dissolves and results in formation of microporous membrane *in situ*, as shown in **(Fig.4).**

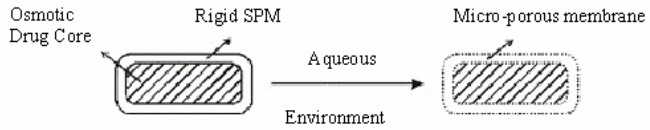

Figure 4: Controlled Porosity Osmotic Pump (CPOP)

A controlled porosity wall can be described as having a sponge ñlike appearance. Generally, materials producing from 5 to 95% pores with a pore size from
10A - 100µm can be used [9,16,19,20]**.** The resulting membrane is substantially permeable to both water and dissolved solute. Water-soluble additives used for this
purpose are dimethyl sulfone, saccharides, amino acids, sorbotil, etc.[21]**.** Ying-Ku Lin (2003) studied the release mechanism of drug with moderate to high solubility with various solubility modulators **[**22]**.**

Osmotic Pump for Insoluble Drugs: It comprises of coating the particles of osmotic agent (osmogens) with an elastic semi permeable film. These particles are mixed with the insoluble drug and compressed in the form of a tablet, which is subsequently coated with a semipermeable membrane, and an orifice is created in the membrane. Following its contact with the aqueous environment, water is drawn through the two membranes into the osmotic agent particles, which then swell and push the insoluble drug hydrostatically via the delivery orifice [23] **.**

Multiparticulate Delayed-Release System: In this system, pellets containing pure drug with or without osmotic agent are coated with a semi-permeable membrane like cellulose acetate. On contact with the aqueous environment, water penetrates into the core and forms a saturated solution of soluble components. The osmotic pressure gradient induces a water influx, leading to rapid expansion of the membrane and formation of the pores. The release of osmotic ingredient(s) and the drug through these pores tend to follow zero-order kinetics. In a study by Schultz and Kleinebudde [24], lag time and dissolution rates were found to be dependent on the coating level and osmotic properties of the dissolution medium.

Monolithic Osmotic Systems: It constitutes a simple dispersion of a water-soluble agent in a polymeric matrix. When the system comes in contact with the aqueous environment, water imbibitions by the active agent takes place rupturing the polymeric matrix capsule surrounding the drug, thus liberating it to the outside environment. Initially, this process occurs at the outer environment of the polymer matrix, but gradually proceeds towards the interior of the matrix in a serial fashion. However, this system fails if more than 20 to 30% volume of the active agent is incorporated into the device, as above this level, significant contribution from the simple leaching of the substance takes place[25].

Colon Targeted Oral Osmotic System (OROS-CT): OROS-CT is used as once or twice a day formulation for targeted delivery of drugs to the colon. It is a system with 5-6 enteric-coated push-pull osmotic units filled in hard gelatin capsule for targeted colonic drug delivery [26]. After coming in contact with GI fluids, the gelatin capsule dissolves and the enteric coating prevents the entry of fluids from stomach into the system **(Figure 5)**.

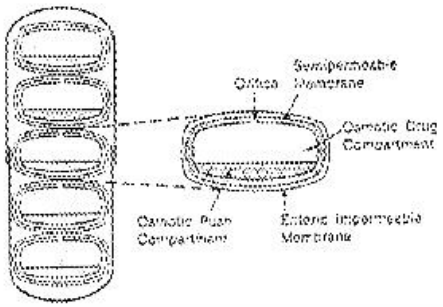

Figure 5: Cross-sectional Diagram of OROS-CT Delivery System.

As the OROS-CT 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, flow-able gel is formed in the drug compartment, which is pushed out of the orifice at the rate precisely controlled by the rate of water transport across the semi-permeable membrane. About 80% of the drug is delivered to the large intestine by OROS-CT.

Sandwiched Osmotic Tablets (SOTS): It is composed of polymeric push layer sandwiched between two drug layers with two delivery orifices [1]. When placed in the aqueous environment **(Figure 6)**[27] the middle push layer containing the swelling agents, swells and the drug is released from the delivery orifices. The advantage of this type of system is that the drug is released from the two orifices situated on opposite sides of the tablet and thus SOTS can be suitable for drugs prone to cause local irritation of the gastric mucosa.

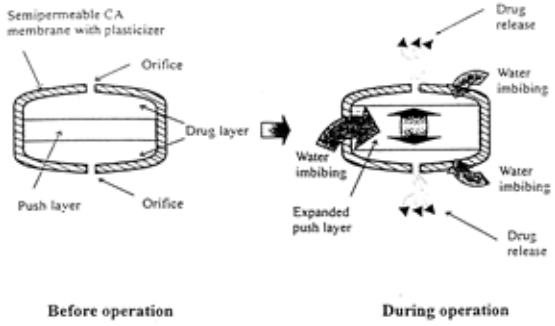

Figure 6: Schematic Diagram of Sandwiched Osmotic Tablet (SOTS)

Liquid Oral Osmotic System (L-OROS): Various L- OROS systems available to provide controlled delivery of liquid drug formulations include L-OROS hard cap, L-OROS soft cap and a delayed liquid bolus delivery system. Each of these systems includes a liquid drug layer, an osmotic engine or push layer and a semi- permeable coating **(Figure 7)**.

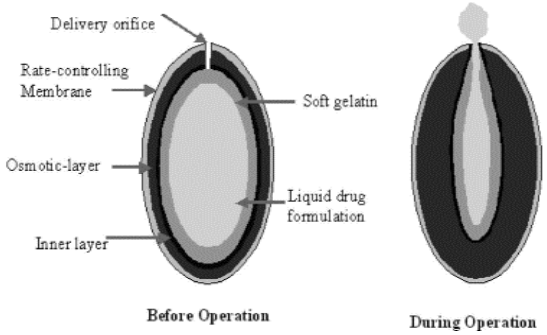

Figure 7 Cross-sectional Diagram of Liquid Oral Osmotic System (L-OROS)

When the system is in contact with the aqueous environment, water permeates across the rate- controlling membrane and activates the osmotic layer. The expansion of the osmotic layer results in the development of hydrostatic pressure inside the system,

there by forcing the liquid formulation to be delivered at the delivery orifice[1]**.** Whereas, L-OROS hard cap and L-OROS soft cap systems are designed to provide continuous drug delivery, the L-OROS delayed liquid bolus delivery system is designed to deliver a pulse of liquid drug [14].

Osmotic Matrix Tablet (OSMAT): It is a novel osmotically driven matrix system, which utilizes the property of hydrophilic polymers to swell and gel in aqueous medium forming a semi-permeable in situ. Release from such a matrix system containing an osmogent could, therefore, be modulated by the osmotic phenomenon. OSMAT thus judiciously combines both matrix and osmotic characteristics resulting in a quantum improvement in drug delivery from swellable matrix systems. Osmotic matrix tablets are very simple to manufacture and precludes the procedures of coating a semi-permeable membrane and drilling a delivery orifice. It is a low cost technology and can be adapted to a wide variety of drugs [6]**.**

Formulation aspects

The various formulation factors affecting drug release from oral osmotic pumps are:

Drug solubility

Solubility of the drug selected for osmotic formulation is a very important factor as the solubility is directly proportional to the release kinetics from the osmotic system. Drugs with high and low water solubility do not form a good candidate for osmotic delivery. If needed, the solubility of drug in the core can be modulated by incorporating suitable solubility modulators to control the release of drug from the osmotic system [14, 28, 29, 30, and 31]**.** Assuming a tablet core of pure drug, the fraction of core released with zero-order kinetics is given by the following equation

$$F(z) = 1 - S/\grave{0} \quad \text{...Equation (4)}$$

Where, F (z) is the fraction released by zero-order kinetics, S is the solubility of drug (g/cm^3) , and $\grave{0}$ is the density (g/cm3) of the core tablet. Drugs with a solubility of ≤0.05 g/cm3 would be released with ≥ 95% zero-order kinetics according to Eq. (4) Osmotic pressure

Drugs selected as candidate for formulation as an osmotic system, should possess osmotic pressure. The release rate of drug from osmotic system is directly proportional to the osmotic pressure of the core formulation [1]. If the drug does not possess sufficient osmotic pressure, an osmogent like sodium chloride, glucose, sucrose, glycine, etc. can be added in the core formulation to control the release of drug from the osmotic system [16]**.**

Delivery orifice

Release of drug from osmotic system is carried out with the help of delivery orifice, thus the size of delivery orifice is a critical factor in controlling the release of drug. The size of the delivery orifice has to be optimized as a small delivery orifice may affect zero order kinetics; but if the delivery orifice is too small, the hydrostatic pressure may not be relieved causing deformation of the system or unpredictable drug release profile, while if delivery orifice is too large, solute diffusion may take place. There are mathematical calculations that can be used to calculate the optimum size of the delivery orifice [10]. Delivery orifice is made in the osmotic system either by mechanical drilling or by laser drilling in the semipermeable membrane of the osmotic system [17]. In case of CPOP, the *in situ* pore formation takes place depending on the concentration of the pore-forming agent in the coating solution [32].

Coating membrane

The choice of a rate-controlling membrane is an important aspect in the formulation development of oral osmotic systems. From Eq. (3), the importance of rate- controlling membrane in the drug release can be recognized. The polymers used for coating of the osmotic system should be semi-permeable in nature. Therefore, any polymer that is permeable to water but impermeable to solute can be used for this purpose. The polymers commonly used for this purpose are cellulose esters such as cellulose acetate, cellulose diacetate, cellulose triacetate, cellulose propionate and cellulose acetate butyrate. Cellulose acetate films are insoluble yet semi permeable and allow water to pass through the coating. Water permeability of cellulose acetate films depends on the amount and type of acetylation on the cellulose backbone [33, 34]. As the acetyl content increases, the permeability decreases, solvent resistance increases and the glass transition temperature increases. To ensure that the coating is able to resist the pressure within the osmotic system, thickness of membrane is usually kept between 200 ñ300 µm [5]**.**

Evaluation of Oral Osmotic Drug Delivery Systems Oral osmotic drug delivery systems can be evaluated using a range of studies [13, 14, and 35]**:**

In Vitro Evaluation

The designed Oral Osmotic Drug Delivery System mainly Osmotic Pump Tablets can be evaluated by:

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[36], flow-through apparatus, etc.

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 widely been 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) [37]. In vivo evaluation can also be performed in healthy human volunteers. Various pharmacokinetic parameters (Cmax, Tmax, AUC and MRT) and relative bioavailability are calculated.

Summary

Osmotic drug delivery systems are based on utilization of osmosis as driving force for drug delivery in a specially engineered core. Osmotic drug delivery system as a dosage form for controlled delivery of drug has gained popularity over time because of the potential advantages like drug delivery at zero order rate, no effect of gastric pH and hydrodynamic condition on release rate, etc. 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. By modulating various formulation aspects, it is possible to use these systems to deliver drugs of diversified nature at a pre-programmed rate. Osmotic drug delivery systems occupy a niche area in oral controlled drug delivery.

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