Review Article CODEN: IJPRNK ISSN: 2277-8713
Karim A. Rana, IJPRBS, 2015; Volume 4(2): 115-129 IJPRBS

INTERNATIONAL JOURNAL OF PHARMACEUTICAL RESEARCH AND BIO-SCIENCE

OSMOTIC DRUG DELIVERY SYSTEM FOR ZERO ORDER KINETIC

KARIM A. RANA, BHAVIN BHIMANI, GHANSHYAM PATEL, DHIREN DASLANIYA, KIRTAN SANGHAVI

Arihant School of Pharmacy & BRI, Adalaj, Gandhinagar

Accepted Date: 17/02/2015; Published Date: 27/04/2015

Abstract: Conventional Drug Delivery Systems Have Little Control Over Their Drug Release And Almost No Control Over The Effective Concentration At The Target Site. The Major Problem Associated With Conventional Drug Delivery System Is Unpredictable Plasma Concentrations. Osmotic Devices Are The Most Promising Strategy Based Systems For Controlled Drug Delivery. They Are The Most Reliable Controlled Drug Delivery Systems And Could Be Employed As Oral Drug Delivery Systems. The Present Review Is Concerned With The Study Of Drug Release Systems Which Are Tablets Coated With Walls Of Controlled Porosity. When These Systems Are Exposed To Water, Low Levels Of Water Soluble Additive Is Leached From Polymeric Material I.E. Semi Permeable Membrane And Drug Releases In A Controlled Manner Over An Extended Period Of Time. Drug Delivery From This System Is Not Influenced By The Different Physiological Factors Within The Gut Lumen And The Release Characteristics Can Be Predicted Easily From The Known Properties Of The Drug And The Dosage Form. In This Paper, Various Types Of Osmotically Controlled Drug Delivery Systems Have Been Discussed.

Keywords: Osmotic Pump, Controlled-Porosity Osmotic Pump Tablet.

PAPER-QR CODE

Corresponding Author: MR. KARIM A. RANA

Access Online On:

www.ijprbs.com

How to Cite This Article:

Karim A. Rana, IJPRBS, 2015; Volume 4(2): 115-129

INTRODUCTION [1-5]

Many conventional drug delivery systems have been designed by various researchers to modulate the release a drug over an extended period of time and release (1). The rate and extent of drug absorption from conventional formulations may vary greatly depending on the factors such as physico-chemical properties of the drug, presence of excipients, physiological factors such as presence or absence of food, pH of the gastro-intestinal tract (GI) and so on (2). However, drug release from oral controlled release dosage forms may be affected by pH, GI motility and presence of food in the GI tract (3). Drugs can be delivered in a controlled pattern over a long period of time by the process of osmosis. Drug delivery from this system is not influenced by the different physiological factors within the gut lumen and the release characteristics can be predicted easily from the known properties of the drug and the dosage form (4). Osmotically controlled drug delivery system, deliver the drug in a large extent and the delivery nature 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. Osmotically controlled oral drug delivery systems utilize osmotic pressure for controlled delivery of active agents (5). Among the controlled release devices, osmotically controlled hold a stable place because of its reliability to deliver the API at predetermined zero order rate for prolonged period of time so these are used as the standard dosage forms for the constant delivery of contents. Osmotic Pump 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 . Recently, osmotic tablets have been developed in which the delivery orifice is formed by the incorporation of a leachable component in the coating. Once the tablet comes in contact with the aqueous environment, the water-soluble component dissolves, and an osmotic pumping system results. Subsequently, water diffuses into the core through the micro-porous membrane, setting up an osmotic gradient and thereby controlling the release of drug.

Advantages [6,7]

There are various no of advantages of ODDS which have been listed below:-

- Decrease frequency of dosing.
- Reduce the rate of rise of drug concentration in the body.
- Delivery may be pulsed or desired if required.
- Delivery ratio is independent of pH of the environment.
- Delivery is independent of hydrodynamic condition, this suggest that drug delivery is independent of G.I. motility.
- Sustained and consistence blood level of drug within the therapeutic window.

- Improve patient compliance.
- High degree of in vitro- in vivo correlation is obtained in osmotic system.
- Reduce side effect.
- Delivery rate is also independent of delivery orifice size within the limit.

Disadvantage [8,9]

- Special equipment is required for making an orifice in the system.
- Expensive.
- Toxicity due to dose dumping.
- Additional patient education and counseling is required.
- Rapid development of tolerance.
- Hypersensitivity reaction may occur after implantation.
- Poor systemic availability in general.
- It may cause gastric irritation or ulcer due to release of saturated solution of drug.

Limitation [10, 11]

OCODDS have produced significant clinical benefit in various therapeutic areas .Some system have enhanced patient compliance, while other has minimized the side effect of their active compounds. However some limitations of OCODDS have been reported.

- Slightly higher cost of good than matrix tablet or multi particulates ion capsule dosage form.
- Gastro intestinal obstruction cases have been observed with the patient receiving Nifedipine GITS tablet.
- Another case was reported for osmosis (Indomethacin OROS) which was first introduced in the United Kingdom in 1983 .A few month later after its introduction frequent incidences of serious gastrointestinal reaction was observed leading to osmosis withdrawal. Various explanations were given based on the toxic effect of KCl used in osmosis.
- Magnetic resonance imaging (MRI) of tablet elucidate that non-uniform coating leads to different pattern of drug release among the batches.

OSMOSIS [12,13,14]

Osmosis refers to the process of movement of solvent molecules from lower concentration to higher concentration across a semi permeable membrane. Osmosis is the phenomenon that makes controlled drug delivery a reality. Osmotic pressure created due to imbibitions of fluid from external environment into the dosage form regulates delivery of drug from osmotic device. Rate of drug delivery from osmotic pump is directly proportional to the osmotic pressure developed due to imbibitions of fluids by osmogen. Osmotic pressure is a colligative

property of a solution in which the magnitude of osmotic pressure of solution is independent on the number of discrete entities of solute present in the solution. Hence the release rate of drugs from osmotic dispensing devices is dependent on the solubility and molecular weight and activity coefficient of solute (osmogent).

Principles of Osmosis [12,13,14]

The first report of an osmotic effect dates to Abbenollet {1748}. But Pfeffer obtained the first quantitative measurement in 1877. In Pfeffer experiment a membrane permeable to water but impermeable to sugar is used to separate a sugar solution from pure water. A flow of water then takes place into the sugar solution that cannot be halted until a pressure π is applied to the sugar solution. Pfeffer showed that this pressure, the osmotic pressure π of the sugar solution is directly proportional to the solution concentration and the absolute temperature. Within few years, Vant Hoff had shown the analogy between these results and ideal gas laws by the expression

$\pi = \emptyset\ c\ RT$

Where, π = Osmotic pressure,

Ø = osmotic coefficient,

c = molar concentration,

R = gas constant

T = Absolute temperature.

Osmotic pressure is a colligative property, which depends on concentration of solute that contributes to osmotic pressure. Solutions of different concentrations having the same solute and solvent system exhibit an osmotic pressure proportional to their concentrations. Thus a constant osmotic pressure, and thereby a constant influx of water can be achieved by an osmotic delivery system that results in a constant zero order release rate of drug. Osmotic pressure for concentrated solution of soluble solutes commonly used in controlled release formulation are extremely high ranging from 30 atm for sodium phosphate up to 500 atm for a lactose-fructose mixture, as their osmotic pressure can produce high water flow across semipermeable membrane. The osmotic water flow through a membrane is given by the equation

$dv\backslash dt = A\ Q\ \Delta\ \pi\backslash\ L$

Where,

dv\dt = water flow across the membrane of area A in cm2,

L = thickness,

Q = permeability

Δ π = the osmotic pressure difference between the two solutions on either side of the membrane. This equation is strictly for completely perm selective membrane that is membrane permeable to water but completely impermeable to osmotic agent.

BASIC COMPONENTS OF OSMOTIC DRIG DELIVERY SYSTEMS: [15-18]

The basic components of osmotic drug delivery systems are as follows:

- Drug
- Osmotic agent
- Semi permeable membrane
- Pore former
- Plasticizer
- Wicking agent
- Coating solvents

1. DRUG:

All drugs are not suitable candidate for osmotic system as prolonged action medication. Drug with biological half life > 12 hours E.g. Diazepam and drug which have very short half life i.e. < 1 hour E.g. Penicillin G, Furosemide are not suitable candidate for osmotic controlled release. Drug which have biological half-life in between 1-6 hours and which is used for prolonged cure of diseases are ideal drugs for osmotic systems. A variety of drug candidates such as Glipizide, Carbamazepine, Metoprolol, Oxprenolol, Nifedipine, Diltiazem HCl etc. are formulated as osmotic drug delivery systems.

2. OSMOTIC AGENT:

Osmotic components usually are ionic compounds consisting of either inorganic salts or hydrophilic polymers. Different type of osmogents can be used for such systems are categorized as water – soluble salts of inorganic acids like magnesium chloride or sulphate; lithium, sodium or potassium chloride; sodium or potassium hydrogen phosphate; water – soluble salts of organic acids like sodium and potassium acetate, magnesium succinate, sodium benzoate; carbohydrates like mannose, sucrose, maltose lactose; water –soluble amino acids

and organic polymeric osmogents.The osmotic pressures of saturated solutions of commonly used osmogens are given in Table -1

Compound of mixture	Osmotic pressure(atm)
Laciose – fructose	500
Dextrose – fructose	450
Potassium chloride	245
Fructose	335
Lactose –Dextrose	225
Mannitol- Sucrose	170
Sucrose	150
Mannitol – Lactose	130
Dextrose	82
Potassium Sulphate	39
Mannitol	38
Sodium phosphate tribasic.12H2O	36
Sodium phosphate dibasic.7H20	31
Sodium phosphate dibasic. 12H20	31
Sodium phosphate monobasic.H20	28
Sodium phosphate dibasic. Anhydrous	21

3. SEMI PERMEABLE MEMBRANE:

There are various types of polymers used as semi permeable membrane. The selection of polymer is based on the solubility of drug as well as amount and rate of drug to be released from pump. Cellulose acetate is a commonly employed as semipermeable polymer for the preparation of osmotic pumps. It is available in different acetyl content of 32% and 38%. A part

from cellulose derivative, some other polymers such as agar acetate, amylase triacetate, betaglucan acetate, poly (vinyl) ether co-polymers, Poly (orthoesters) poly acetals and selectively permeable poly (glycolic acid) and poly (lactic acid) derivatives can be used as semi permeable film forming materials.

Ideal Properties of Semi Permeable Membrane

1. It should be adequately thick to withstand the pressure generated within the device.

2. It should have enough wet strength and water permeability.

3. It should be biocompatible.

4. It should be rigid and non-swelling.

4. PORE FORMER:

These agents are particularly used in the development of pump for poorly water-soluble drugs and in controlled porosity tablets. These pore forming agents can cause the formation of micro porous membrane. The pore formers can be inorganic or organic and solid or liquid in nature. Some examples of pore former are alkaline metals such as sodium chloride, sodium bromide, potassium chloride, potassium phosphate, alkaline earth metals such as calcium chloride and calcium nitrate. Carbohydrates such as sucrose, glucose, fructose, lactose, mannitol.

5. PLASTICIZERS:

Plasticizers have a crucial role to play in the formation of a film coating and its ultimate structure. Plasticizer increases the wetability, flexibility and permeability of fluids. They can change viscous-elastic behavior of polymers and these changes may affect the permeability of the polymeric films. Plasticizers can have a marked effect on both qualitatively and quantitatively on the release of active materials from modified release dosage forms where they are incorporated into the rate-controlling membrane.

Some of the plasticizers used are as below:

For low permeability- Polyethylene glycols, Glycolate, Glycerolate, Myristates, Ethylene glycol monoacetate; and diacetate. For more permeable films- Tri ethyl, Diethyl tartarate or Diacetin.

6. WICKING AGENTS:

It is defined as a material with the ability to draw water into porous network of a delivery orifice. A wicking agent has ability to draw water into the porous network of a delivery device. A wicking agent is of either swellable or non-swellable in nature. The function of wicking agent is

to carry water to surfaces inside the core of tablet, thereby creating channels or network of increased surface area. Materials used for wicking agent includes colloidal silicon dioxide, kaolin, alumina, sodium lauryl sulphate, low molecular weight poly vinyl pyrrolidine, bentonite etc.

7. COATING SOLVENT:

The primary function of solvent system is to dissolve or disperse the polymer and other additives and convey them to substrate surface.Solvents suitable for making polymeric solution that is used for manufacturing the wall of the osmotic device include inert inorganic and organic solvents. The various types of solvents and their combinations are as follows: methylene chloride, ethanol, isopropyl alcohol, butyl alcohol, ethyl acetate, cyclohexane, carbon tetrachloride and water. The mixture of solvents such as acetone- methanol (80:20), methylene chloride- methanol (79:21), methylene chloride-methanol-water (75:22:3) can be used.

The ideal solvent system should have following properties.

- It should easily and completely dissolve the polymer.
- It should easily disperse other coating components into solvent system.
- It should not give extremely viscous solution with small concentration of polymer (2-10%).
- It should be odorless, colorless, tasteless, inexpensive, nontoxic, and non-irritant.
- It should have rapid drying rate.

CLASSIFICATION OF ODDS [19-28]

Type of Osmotic Pump	Composition	Mechanism of Action	Advantages
Single Chamber Osmotic Pumps Elementary osmotic pump (EOP)	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	Suitable for delivery of drugs having moderate water solubility

		orifice present in the membrane.	
Osmotic Pump with Non-Expanding Second Chamber	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)	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
Controlled porosity osmotic pump	The controlled porosity osmotic pump tablet is coated with semipermeable membrane containing leach able pore forming agents	The drug release achieved through the pores which are formed in semipermeable wall in situ during operation . In this system , the drug ,after dissolution inside the core,is released from osmotic pump tablet by hydrostatic pressure and diffusion through pore screened by dissolution of pore former incorporated in membrane. the hydrostatic pressure is	A)it follow zero order kinetic thus better control over the drug's in vivo performance is possible B)the drug release is independent of the gastric pH and hydrodynamic conditions. C)the delivery rate of drug from these systems is highly predictable and can be programmed by modulating the turms D)drug release from these

		created either by an osmotic agent or by drug itself or by tablet component, after water is imbided across semipermeable membrane .the release rate from these type of systems on coating thickness ,level of leachable components in the coating,solubility of drug in the tablet core, and osmotic pressure diffrence across the membrane but it is independent of ph and agitation of the release media.	systems exhibits significant in-vivo in-vivocorrelation[IVIVC]within specific limits E)Production scale up is easy and No need of drilling.
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
Sandwiched osmotic tablet (SOTS)	Tablet core consisting of a middle push layer and two attached drug layers is coated with a SPM.	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.	System delivers drug from two opposite orifices, rather from the single orifice of the PPOP

Liquid OROS controlled release system (L-OROS)	Two types: ***L-OROS Soft cap and L-OROS hard cap.*** 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.	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.	To deliver APIs as liquid formulations and combine the benefits of extended release with high bio-availability. Suitable for controlled delivery of **lipophilic APIs**
Osmotic bursting osmotic pump	Similar to an EOP expect delivery orifice is absent and size may be smaller	When it is placed in an aqueous environment, water is imbibed and hydraulic pressure is built up inside until the wall rupture and the content are released to the environment	This system is useful to provide pulsated release.
OROS Push-Stick Technology	It consists of a bilayer capsule shaped tablet.	Similar as PPOP tablets	Provides the greatest benefit for compounds with low water solubility and dosage greater than 150 mg.
Multiparticulate	Pellets	The osmotic pressure	

Delayed-Release System	containing drug with or without osmotic agent are coated with an SPM.	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	

EVALUATION OF OSMOTIC TABLET

- Hardness
- thickness
- friability
- weight uniformity
- drug content
- *in vitro* dissolution study
- effect of osmotic pressure
- effect of PH on drug release
- stability study
- zero order release kinetic

CONCLUSION:

It can be concluded that the oral controlled porosity osmotic pump system comprising a compressed tablet coated with a semi permeable membrane is simple to prepare with no drilling required and can be used in the field of controlled delivery of drugs. In osmotic delivery systems, osmotic pressure provides the driving force for drug release. Increasing pressure inside the dosage form from water incursion causes the drug to release from the system. The major advantage include precise control of zero order release over an extended time period-consistent release rates can be achieved irrespective of the environment factors at the delivery site. Drug delivery from this system is not influenced by the different physiological factors within the gut lumen and the release characteristics can be predicted easily from the known properties of the drug and the dosage form.

REFRENCES

1. Madhavi BB, Nath AR, Banji D, Ramalingam R, Madhu MN, Kumar DS. Osmotic drug delivery system: a review. Pharmakine, dec 2009; 2: 5-14.

2. Mishra B, Makesh BK, Sankar C. Oral push-pull osmotic pumps of pentazocine hydrochloride: development and evaluation. Ind J Pharm Sci, 2006; 68:1:85-87.

3. Verma RK, Krishna DM, Garg S. Formulation aspects in the development of osmotically controlled oral drug delivery systems. J Control Release, 2002; 79:7–27

4. YANG Xing-Gang, ZHANG Guo-Hua, LI Wei, PENG Bo, LIU Zhi-Dong, PAN Wei-San. Design and Evaluation of Jingzhiguanxin Monolithic Osmotic Pump Tablet. Chem Pharm Bull, 2006; 54:4:465-469.

5. Makhija Sapna N, Vavia Pradeep R. Controlled porosity osmotic pump-based controlled release systems of pseudoephedrine I: Cellulose acetate as a semipermeable membrane. J Control Release, 2003;89:5–18

6. Bhatt P Padmanabh. Osmotic drug delivery system for poorly soluble drug, Pharma venture ltd. (2004).

7. Das N. and Das S, Controlled release of Oral Dosage Forms Formulation. Fill & Finish;2003:10-5

8. Verma RK, Mishra B, GargS.Osmotically controlled drug delivery. Drug DevInd Pharm.2000;26(7):695-70 .

9. Vyas SP , Khar RK,Controlled Drug delivery concepts and advaces osmotically regulated system, first edition. P.477-501.

10. Sreenivasa Rao B , Ravikumar N, Maduri K, Narayanan PS and Ramama Murthy KV,(2001),Osmotic Drug Delivery system- An Overview. The eastern pharmacist, 21-28.

11. Vyas SP, (2002), Controlled Drug Delivery Concepts and Advances, 3rd ed. CBS Publisher, New Delhi, 1-10,477-502.

12. Stuti Gupta, Ravindra Pal Singh, Rohitashva Sharma, Renu Kalyanwat and Priyanka lokwani1, osmotic pumps: a review, pharmacieglobale ,international journal of comprehensive pharmacy, issn 0976-8157

13. RajanK.Verma,DiviMuraliKrishna,SanjayGarg"Formulation aspects in the development of osmotically controlled oral drug delivery system", journal of controlled release 79(2002) 7-27 .

14. Jain NK, Advances in Noval and controlled delivery", p.18-39 .

15. Nikam PH, Kareparamban JA, Jadav AP and Kadam VJ, (2012), Osmotic Pump: A Reliable Drug Delivery System. Res. J. Pharm. Bio. Chem. Sci, 3,478-493.

16. Singla D, Hari Kumar SL, Nirmala G, (2012), Osmotic Pump Drug Delivery- A Novel Approach. Int. J. Res. Pharm. Chem. Sci, 2, 661-670.

17. Martin W and Bbodmeier R, (2001), Influence of plasticization time, curing conditions, storage time and core properties on the drug release from aqua coat-coated pellets, Pharm.Dev.Thec, 6,325-331.

18. Thakor RS, Majmudar FD, Patel JK, Rajaput GC. Review: Osmotic drug delivery systems current scenario. J of Pharm Res 2010; 3(4): 771-775.

19. Verma RK, Mishra B, Garg S. Osmotically controlled oral drug delivery. Drug Dev lnd Pharm 2000; 26:695-708.

20. Edavalath S, Shivanand K, Prakasam K, Formulation development and optimization of controlled porosity osmotic pump tablets of Diclofenac Sodium. Int. J. of Pharm. and Pharma. Sci. 2011; 3:438-446

21. sagar lahu ,anand dayaram savkare,controlled porosity osmotic pump : A review IJPRD,2014;vol 5: feb-2014 (74)

22. Thakor RS, Majmudar FD, Patel JK, Rajaput GC. Review: Osmotic drug delivery systems current scenario. J of Pharm Res 2010; 3(4): 771-775.

23. Verma RK, Mishra B, Garg S. Osmotically controlled oral drug delivery. Drug Dev lnd Pharm 2000; 26:695-708.

24. Liu L, Ku J, Khang G, Lee B, Rhee JM, Lee HB. Nifedipine controlled delivery by sandwiched osmotic tablet system. J Cont Rel 2000; 68:145–156

25. Dong L, Shafi K, Wan J, Wong P. A novel osmotic delivery system: L-OROS softcap. Proceedings of the 27th International Symposium on Controlled Release of Bioactive Materials; 2000 July 7–13, Paris, France. Controlled Release Society; 2000.

26. Dong L, Wong P, Espinal S. L-OROS HARDCAP: A new osmotic delivery system for controlled release of liquid formulation. Proceedings of the 28th International Symposium on Controlled Release of Bioactive Materials; 2001 June 23–27; San Diego, CA. Controlled Release Society; 2001.

27. Verma RK, Krishna DM, Garg S. Formulation aspects in the development of osmotically controlled oral drug delivery systems. J Cont Rel 2002; 79:7–27.

28. A Review On Oral Osmotically Driven Systems, Kunal N Patel, Dr. Tejal A Mehta, International Journal of Pharmacy and Pharmaceutical Sciences Vol 5, Issue 3, 2013 .