ISSN: 2277-8713
Hardik Prajapati, IJPRBS, 2012: Volume1 (3):158-194 *IJPRBS*

REVIEW ARTICLE

INTERNATIONAL JOURNAL OF PHARMACEUTICAL RESEARCH AND BIO-SCIENCE

A Path for Horizing Your Innovative Work

A REVIEW ON RECENT INNOVATION IN OSMOTICALLY CONTROLLED DRUG DELIVERY SYSTEM

***PRAJAPATI H. M., PRAJAPATI S. T., PATEL C. N.**

Department of Pharmaceutics and Pharmaceutical Technology, Shri Sarvajanik Pharmacy College, Near Arvind Baug, Mehsana-384001, Gujarat, India.

Corresponding Author Email: **hardik9127@yahoo.com**

Accepted Date: 08/06/2012 **Publish Date: 27/06/2012**

Abstract: Conventional drug delivery systems have slight control over their drug release and almost no control over the effective concentration at the target site. This kind of dosing pattern may result in constantly changing, unpredictable plasma concentrations. Drugs can be delivered in a controlled pattern over a long period of time by the controlled or modified release drug delivery systems. They include dosage forms for oral and transdermal administration as well as injectable and implantable systems. For most of drugs, oral route remains as the most acceptable route of administration. Certain molecules may have low oral bioavailability because of solubility or permeability limitations. Development of an extended release dosage form also requires reasonable absorption throughout the gastro-intestinal tract (GIT). Among the available techniques to improve the bioavailability of these drugs fabrication of osmotic drug delivery system is the most appropriate one. Osmotic drug delivery systems release the drug with the zero order kinetics which does not depend on the initial concentration and the physiological factors of GIT. This review brings out new technologies, fabrication and recent clinical research in osmotic drug delivery.

Keywords: Osmotic pump, osmotic pressure, semipermeable membrane, osmogent, leachable pore formers.

INTRODUCTION

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 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 [6]. Subsequently, water diffuses into the core through the microporous membrane, setting up an osmotic gradient and thereby controlling the release of drug [7]. 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 semi permeable membrane, which is permeable only to the solvent but impermeable to the solute.

ADVANTAGES

The following advantages have contributed to the popularity of osmotic drug delivery systems[8, 9].

1. The delivery rate of zero order is achievable with osmotic system.
2. Delivery may be delayed or pulsed, if desired.

3. Higher release rates are possible with osmotic system compared with conventional diffusion-controlled delivery system.
4. The release rate of osmotic system is highly predictable.
5. For oral osmotic system, drug release is independent to gastric pH and hydrodynamic condition.
6. The release from osmotic system is minimally affected by presence of food in gastrointestinal tract.
7. A high degree of *in vivo-in vitro* correlation is obtained in osmotic system.
8. Improve patient compliance with reduced frequency.

HISTORICAL ASPECTS OF OSMOTIC PUMPS

About 75 years after discovery of the osmosis principle, it was first used in the design of drug delivery systems [10]. 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 semi permeable membrane. The difference in osmotic pressure across the membrane moves water from the water chamber into the salt chamber. 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. The pumping rate of this push-pull pump is given by the equation.

$$dM/dt = dV/dt \times c$$

In general, this equation, with or without some modifications, applies to all other type of osmotic systems.

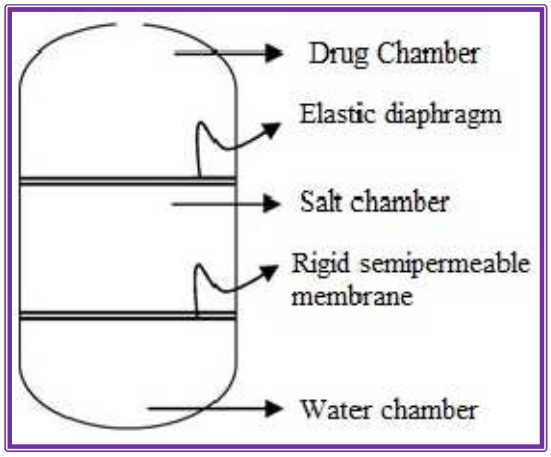

Figure 1: Rose-Nelson pump

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. It has a salt chamber containing a fluid solution with excess solid salt. Recent modification in Higuchi-Leeper pump accommodated pulsatile drug delivery. The pulsatile release was achieved by the production of a critical pressure at which the delivery orifice opens and releases the drug [11]. This pump comprises a rigid, rate controlling outer semi permeable membrane surrounding a solid layer of salt coated on the inside by an elastic diaphragm and on the outside by the membrane. In use, water is osmotically drawn by the salt chamber, forcing drug from the drug chamber [12].

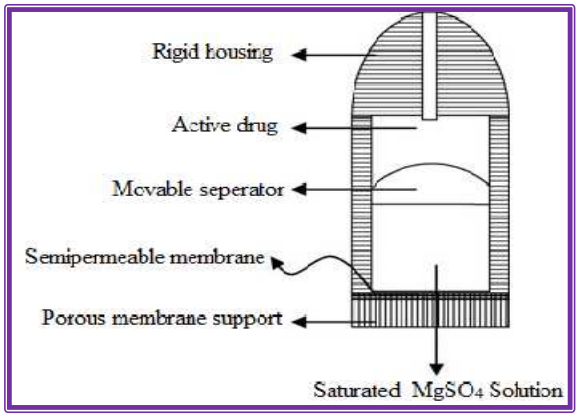

Figure 2 Higuchi-Leeper pump

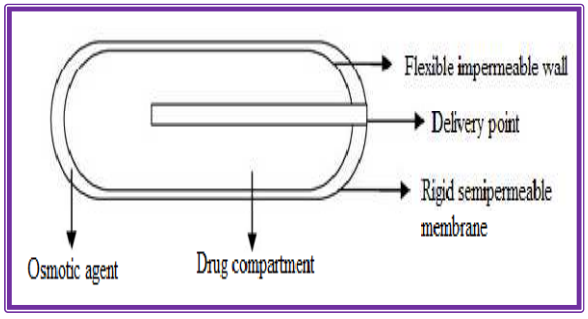

Figure 3 Theeuwes miniature osmotic pump

The pump consists of an osmotic core containing the drug, surrounded by a semi permeable membrane with a delivery orifice. When this pump is exposed to water, the core imbibes water osmotically at a controlled rate, determined by the membrane permeability to water and by the osmotic pressure of the core formulation. As the membrane is nonexpendable, the increase in volume caused by the imbibition of water leads to the development of hydrostatic pressure inside the tablet. This pressure is relieved by the flow of saturated solution out of the device through the delivery orifice. This residual dissolved agent continues to be delivered at a declining rate until the osmotic pressure inside and outside the tablet is equal. Normally, the EOP delivers 60-80% of its contents at a constant rate, and there is a short lag time of 30-60 min as the system hydrates before zero order delivery from the EOP is obtained[13].

KEY PARAMETERS THAT INFLUENCE THE DESIGN OF OSMOTIC CONTROLLED DRUG DELIVERY SYSTEMS

Orifice size

To achieve an optimal zero-order delivery profile, the cross-sectional area of the orifice must be smaller than a maximum size to minimize drug delivery by diffusion through the orifice. Furthermore, the area must be sufficiently large, above a minimum size to minimize hydrostatic pressure buildup in the system. Otherwise, the hydrostatic pressure can deform 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 [14, 15]. Methods to create a delivery orifice in the osmotic tablet coating are:

- Mechanical drill
- Laser drill: This technology is well established for producing sub-millimeter size hole in tablet. Normally CO_2 beam (with output wavelength of 10.6µ) is used for drilling purpose [16, 17]
- Indentation that is not covered during coating process [18]: Indentation made in core tablet by using modified punches having needle on upper punch.
- Use of leachable substances in the semipermeable coating: e.g. controlled porosity osmotic pump.

Solubility

The release rate depends on the solubility of the solute inside the drug delivery system. Therefore, drugs should have sufficient solubility to be delivered by osmotic delivery. In the case of low solubility compounds, several alternate strategies may be employed. Broadly, the approaches can be divided into two categories. First, swellable polymers can be added that result in the delivery of poorly soluble drugs in the form of a suspension [19]. Second, the drug solubility can be modified employing different methods such as co compression of the drug with other excipients, which improve the solubility [20]. For example, cyclodextrin can be included in the formulation to enhance drug solubility[21]. Additionally, alternative salt forms of the drug can be employed to modulate solubility to a reasonable level. In one case, the solubility of oxprenolol is decreased by preparing its succinate salt so that a reduced saturation concentration is maintained[22].

Osmotic pressure

The osmotic pressure π directly affects the release rate. To achieve a zero-order release rate, it is essential to keep π constant by maintaining a saturated solute solution. Many times, the osmotic pressure generated by the saturated drug solution may not be sufficient to achieve the required driving force. In this case, other osmotic agents are added that enhance osmotic pressure. For

example, addition of bicarbonate salt not only provides the necessary osmotic gradient but also prevents clogging of the orifice by precipitated drug by producing an effervescent action in acidic media [23, 24].

Semipermeable membrane

Since the semipermeable membrane is permeable to water and not to ions, the release rate is essentially independent of the pH of the environment. Additionally, the drug dissolution process takes place inside the delivery system, completely separated from the environment [25].

Table 1.

Osmotic pressures of saturated solution of commonly used osmogents

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

Basic Components Required for Osmotic Pump:

a) Drug
b) Osmotic agent
c) Semipermeable membrane
d) Channeling agent or pore forming agent
e) Flux regulator
f) Wicking agent
g) Coating solvent
h) Plasticizer

a. Criteria for selection of a drug:

- Short biological half life (2-6 hour)
- High potency
- Required for prolonged treatment (e.g. nifedipine, verapamil, glipizide, chlorpromazine hydrochloride.)

Vyas.P. *et al* (2004) developed an oral osmotic system which can deliver theophylline and salbutamol sulphate simultaneously for extended period of time and characterized it. An optimized system was selected to study the effect of concentration of pore forming agents and orifice diameter on the release of the drugs. The release profiles of both drugs were satisfactory when compared with marketed controlled release formulations [26].

Roger A. Rajewski *et al* (2004) investigated the application of controlled-porosity osmotic pump tablet (OPT) utilizing (SBE)7m --CD both as a solubilizer and an osmotic agent for drugs with varying physical properties. OPTs utilizing (SBE)7m --CD were prepared for five poorly soluble drugs such as prednisolone, estradiol, naproxen, indomethacine and chlorpromazine and for two highly water soluble drugs such as diltiazem hydrochloride and salbutamol sulfate. It was found that for the soluble drugs (SBE)7m --CD acts primarily as an osmotic and an OPT control agent. Significantly, (SBE) 7m --CD not only enhances the delivery of poorly soluble drugs from OPTs but acts as controlling excipients for soluble drugs such that the release rate, corrected for tablet surface area, of both poorly soluble and soluble drugs are similar [27].

Roger A. Rajewski *et al* (1999) studied the membrane controlling factors responsible for drug release from a controlled-porosity osmotic pump tablet (OPT) that utilizes sulfobutyl ether--cyclodextrin, (SBE) 7m --CD, both as solubilizing agent and osmotic agent. The release rate of chlorpromazine (CLP) from OPTs containing (SBE) 7m --

CD increased with increasing amounts of micronized lactose and decreasing amounts of triethyl citrate. The effect of lactose particle size in the membrane on drug release was studied[28].

b. Osmotic agent

Polymeric osmogents are mainly used in the fabrication of osmotically controlled drug delivery systems and other modified devices for controlled release of relatively insoluble drugs. Osmotic pressures for concentrated solution of soluble solutes commonly used in controlled release formulations are extremely high, ranging from 30 atm for sodium phosphate up to 500 atm for a lactose-fructose mixture (table 1). These osmotic pressures can produce high water flows across semipermeable membranes [29]. The osmotic water flow across a membrane is given by the equation,

$$\frac{dv}{dt} = \frac{A\theta\Delta\pi}{l}$$

Where dv/dt, is the rate of water flow across the membrane of area A, thickness *l*, permeabilityθ in $cm^3.cm/cm^2$. h. atm, and $\Delta\pi$[30].

Wright et.al (1992) studied an osmotic controlled release bilayer tablet for water soluble drugs. In their device, the drug compartment containing the drug and an osmopolymer, a low molecular weight CMC (as thixotropic transport means), was placed together side by side with the osmotic compartment which had a higher molecular weight CMC as osmotic agent preferably with another osmotically active compound. Both low and high molecular weight CMC in the device cooperated to exhibit a high level of hydrodynamic and osmotic activity adequate for controlled delivery of the drug over the time with minimum (as little as 3.7%) residual drug left in the device[31].

c. Semipermeable membrane

The membrane should be stable to both outside and inside environments of the device. The membrane must be sufficiently rigid so as to retain its dimensional integrity during the operational lifetime of the device. The membrane should also be relatively impermeable to the contents of dispenser so that osmogent is not lost by diffusion across the membrane. Finally, the membrane must be biocompatible. Some good examples for polymeric materials that form membranes are cellulose esters like cellulose acetate, cellulose acetate butyrate, cellulose triacetate, ethyl cellulose and Eudragits[32].

Ideal properties of semi permeable membrane[33]

The semipermeable membrane must meet some performance criteria,

a. The material must possess sufficient wet strength (10-5 psi) and wet modules so (10-5 psi) as to retain its dimensional integrity during the operational lifetime of device.
b. The membrane must exhibit sufficient water permeability so as to attain water flux rates (dv/dt) in the desired range. The water vapour transmission rate can be used to estimate water flux rate.
c. The reflection co-efficient (θ) or "leakiness" of the osmotic agent should approach the limiting value of unity. But polymer membrane must be more permeable to water.

Hai Bang Lee *et al* (2000) studied the sandwiched osmotic tablet system (SOTS). A sandwiched osmotic tablet core surrounded by a cellulose acetate membrane with two orifices on the surfaces of both sides was successfully prepared for the purpose of delivering nifedipine. The appropriate orifice size was observed in the range of 0.50 – 1.41 mm. It was also found that the drug release rate of SOTS could be increased by incorporating hydrophilic plasticizer in the membrane, whereas it could be decreased by incorporating a hydrophobic plasticizer[34].

Herbig S. M. *et al* (1995) found a new type of asymmetric membrane tablet coatings offering significant advantages over conventional osmotic tablets. These asymmetric-membrane coatings can be used to make osmotic drug-delivery formulations with several unique characteristics. The use of asymmetric-membrane coatings on pharmaceutical tablets is described in this study; the coatings have also been applied to capsules and multi-particulate formulations[35].

d. Channeling agent or leachable pore forming agents

These are the water-soluble components which play an important role in the controlled drug delivery systems. When the dissolution medium comes into contact with the semipermeable membrane it dissolves the channeling agent and forms pores on the semipermeable barrier. Then the dissolution fluid enters the osmotic system and releases the drug in a controlled manner over a long period of time by the process of osmosis. Some examples of channeling agents are polyethylene glycol (PEG) 1450, -mannitol, bovine serum albumin (BSA), diethylphthalate, dibutylphthalate and sorbitol[36-38].

Pradeep Vavia. R *et al* (2003) designed a controlled porosity osmotic pump based on controlled release systems of pseudoephedrine in which cellulose acetate was used as a semipermeable membrane. The effect of pH on drug release was also studied. This system was found to deliver pseudoephedrine at a zero order rate for twelve (12) hrs independent of the environmental pH[39].

Ji-Eon Kim *et al* (2000) studied the effect of various pore formers on the controlled release of an antibacterial agent from a polymeric device. Cefadroxil was chosen as the model antibiotic and was incorporated into a polyurethane matrix by the solvent-casting method. Polyethylene glycol 1450 or -mannitol, or bovine serum albumin (BSA) was used as a pore former. The morphological changes in the matrices before and after release studies were investigated by scanning electron microscopy (SEM). Changing the weight fraction and particle size of the pore formers/drug mixtures could control the release of cefadroxil from the matrix. The release rate of cefadroxil increased as the loading dose of the pore former increased (15<20<25%)[40].

Gaylen Z M. *et al* (1985) studied zero-order release of water-soluble osmotically active agents from tablets coated with controlled-porosity walls. The walls were sponge like in appearance and substantially permeable to both water and dissolved solutes. The rate of release was a function of the wall thickness and the level of leachable pore forming agents. The concept of osmotically actuated drug delivery on an equivalent mass per unit surface area basis was demonstrated[41].

e. Flux regulators

Delivery systems can be designed to regulate the permeability of the fluid by incorporating flux regulating agents in the layer. Hydrophilic substances such as polyethethylene glycols (300 to 6000 Da), polyhydric alcohols, polyalkylene glycols, and the like improve the flux, whereas hydrophobic materials such as phthalates substituted with an alkyl or alkoxy (e.g., diethyl phthalate or dimethoxy ethylphthalate) tend to decrease the flux. Insoluble salts or insoluble oxides, which are substantially water-impermeable materials, also can be used for this purpose [8].

f. Wicking agents

A wicking agent is defined as a material with the ability to draw water into the

porous network of a delivery device. A wicking agent is of either swellable or non-swellable nature. They were characterized by having the ability to undergo physisorption with water. Physisorption is a form of absorption in which the solvent molecules can loosely adhere to surfaces of the wicking agent via Vander Waals interactions between the surface of the wicking agent and the adsorbed molecule. The function of the wicking agent is to carry water to surfaces inside the core of the tablet, thereby creating channels or a network of increased surface area. Materials, which suitably for act as wicking agents include colloidal silicon dioxide, kaolin, titanium dioxide, alumina, niacinamide, sodium lauryl sulphate (SLS), low molecular weight poly vinyl pyrrolidone (PVP), m-pyrol, bentonite, magnesium aluminium silicate, polyester and polyethylene.

g. 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 include 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 [30].

h. Plasticizer

Different types and amount of plasticizers used in coating membrane also have a significant importance in the formulation of osmotic systems. They can change visco-elastic behavior of polymers and these changes may affect the permeability of the polymeric films[8]. Some of the plasticizers used are as below:

- Polyethylene glycols
- Ethylene glycol monoacetate; and diacetate for low permeability
- Tri ethyl citrate
- Diethyl tartarate or Diacetin- for more permeable film

TYPES OF OSMOTIC PUMP

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

1. Osmotic Delivery Systems for Solids[42]

a. Type I: Single compartment. In this design, the drug and the osmotic agent are

located in the same compartment and are surrounded by the semipermeable membrane (SPM). Both the core components are dissolved by water, which enters the core via osmosis. A limitation is the dilution of drug solution with the osmotic solution, which affects the release rate of the drug from the system. Additionally, water-incompatible or water-insoluble drugs cannot be delivered effectively from a single compartment configuration.

b. Type II: Multiple compartments. In this design, drug is separated from the osmotic compartment by an optional flexible film, which is displaced by the increased pressure in the surrounding osmotic compartment, which, in turn, displaces the drug solution or suspension. One main advantage of these systems is their ability to deliver drugs that are incompatible with commonly used electrolytes or osmotic agents.

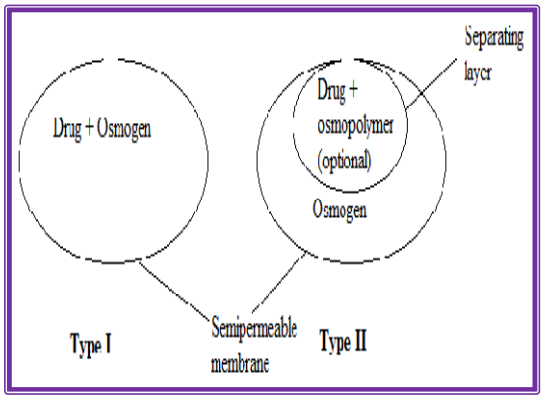

Figure 4: Classification of osmotic delivery systems: Types I and II

2. Osmotic Delivery Systems for Liquids[42]

Active ingredients in liquid form are difficult to deliver from controlled release platforms because they tend to leak in their native form. When the system takes up water from its surroundings, the osmotic layer squeezes the innermost drug reservoir. The increasing internal pressure displaces the liquid from the system via a rupturing soft gelatin capsule.

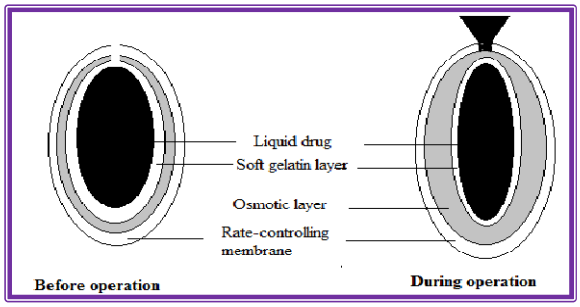

Figure 5: Osmotic delivery system for delivery of a liquid active agent

3. Elementary Osmotic Pump (EOP)[15, 43]

The tablet consists of an osmotic core containing the drug surrounded by a semipermeable membrane laser drilled with delivery orifice. Following ingestion, water in absorbed into system dissolving the drug, and the resulting drug solution is delivered at the same rate as the water entering the tablet. The disadvantages of the elementary pump are that it is only suitable for the delivery of water soluble drugs.

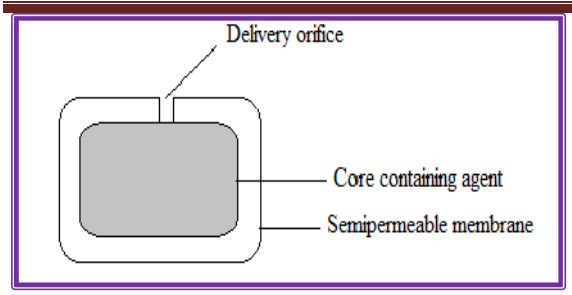

Figure 6: Elementary osmotic pump

4. Push–Pull Osmotic Pump (PPOP)[44]

The push–pull osmotic tablet consists of two layers, one containing the drug and the other an osmotic agent and expandable agent. While the push–pull osmotic tablet operates successfully in delivering water-insoluble drugs, it has a disadvantage that the complicated laser drilling technology should be employed to drill the orifice next to the drug compartment.

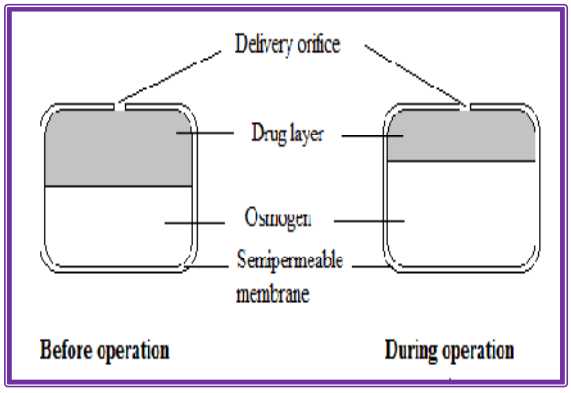

Figure 7: Push pull osmotic pump

5. Controlled Porosity Osmotic Pump

The CPOP contains water soluble additives in coating membrane, which after coming in contact with water; dissolve resulting in an in-situ formation of a microporous membrane. Then the resulting membrane is substantially permeable to both water and dissolved solutes and the mechanism of drug release from this system was found to be primarily osmotic, with simple diffusion playing a minor role[45, 46]. Drug delivery from asymmetric membrane capsule is principally controlled by the osmotic pressure of the core formation. In-situ formed delivery orifice in the asymmetric membrane in mainly responsible for the solubilization in the core for a drug with poor water solubility[47].

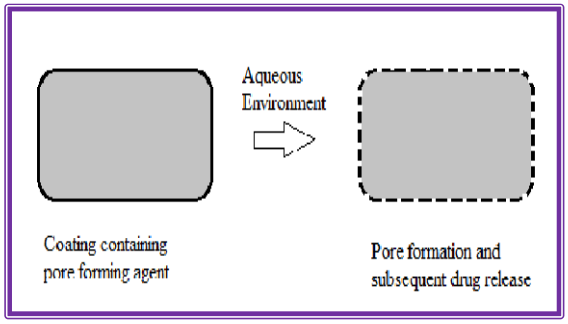

Figure 8: Controlled porosity osmotic pump

6. Osmotic Bursting Osmotic Pump[48]

This system is 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. Varying the thickness as well as the area the semipermeable membrane

can control release of drug. This system is useful to provide pulsated release.

7. Telescopic Capsule for Delayed Release[17, 49]

This device consists of two chambers, the first contains the drug and an exit port, and the second contains an osmotic engine. The bilayer tablet with the osmotic engine is placed into a completed cap part of the capsule with the convex osmotic layer pointed in to the closed end of the cap and the barrier into the closed end of the cap and the barrier layer exposed towards the cap opening. The open end of the filled vessel is fitted inside the open end of the cap, and the two pieces are compressed together until the cap, osmotic bilayer tablet and vessel fit together tightly. As a result, the net flow of environmental fluid driven by the pressure enter the reservoir is minimal and consequently no agent is delivered for the period.

8. OROS-CT [50]

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

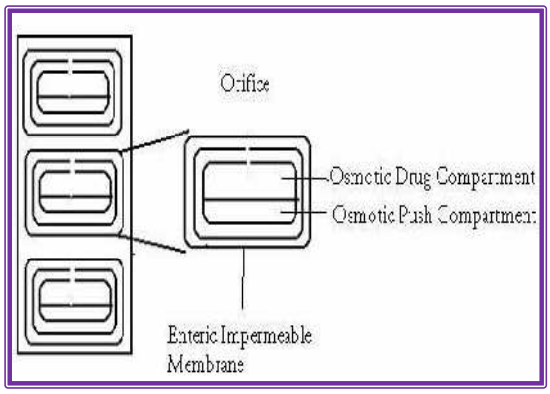

Figure 9: OROS-CT

9. Sandwiched Osmotic Tablets (SOTS)[51]

In this a tablet core composed of polymeric push layer sandwiched between two drug layers with two delivery orifices. When

placed in the aqueous environment the middle push layer containing the swelling agent swells and 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.

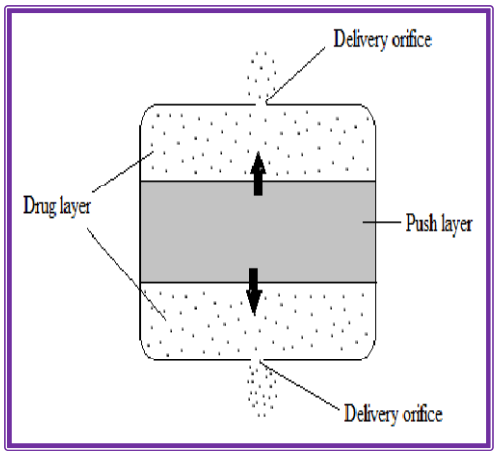

Figure 10: Sandwiched osmotic tablets

10. Longitudinally Compressed Tablet (LCT) Multilayer Formulation[52]

The LCT multilayer formulation is the advanced design. As with the push-pull system it consists of an osmotic push layer and can be configured to contain several drug layers. As with the push-pull formulation, water is absorbed through the exposed semi permeable tablet shell, expanding the push compartment and releasing the drug primarily through the first compartment through the laser drilled orifice at a predetermined controlled rate. The LCT multilayer formulation can also be formulated with different drugs in different layers to provide combination therapy. Similar to the push-pull system, drug delivery by the LCT multilayer formulation can be unaffected by gastric pH, gut motility and the presence of food, depending on where in the GI tract the drug is released.

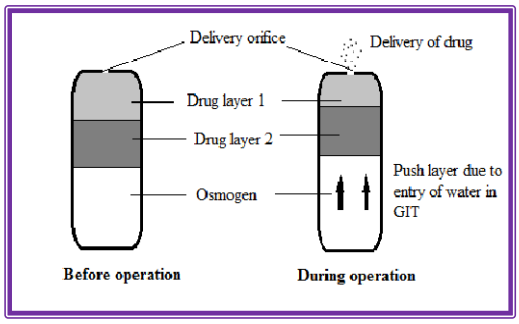

Figure 11: Multilayer osmotic pump

11. Pulsatile Delivery System[53]

These systems are designed according to the circadian rhythm of the body. The principle rationale for the use of pulsatile release is for the drugs where a constant drug release, i.e., a zero order release is not desired. The release of the drug as a pulse after a lag time has to be designed in such a way that a complete and rapid drug release follows the lag time. This type of tablet system consist of core coated with two layer of swelling and rupturable coatings here in they used spray dried lactose and microcrystalline cellulose in drug core and then core was coated with swelling polymer croscarmellose sodium and an outer rupturable layer of ethylcellulose. Pulsatile

systems can be classified into single and multiple-unit systems. In multiple-unit systems, however, the pulsatile release is induced by changing membrane permeability or by coating with a rupturable membrane.

SCIENTIFIC STUDY

Vincent Malaterre et.al studied on the release mechanism underlying the drug delivery from push–pull osmotic pumps (PPOP). The aim of this study was to understand which factors have an effect on the drug delivery for modeling the drug release and to develop a mathematical model predictive of the drug release kinetics. The influence of the drug property was tested on two model drugs, isradipine (ISR) and chlorpheniramine (CPA) which are respectively practically insoluble and freely soluble. Results show that, regardless of the drug properties which do not significantly affect the drug delivery, the release kinetics is mainly controlled by four factors, (i) the PEG proportion in the membrane, (ii) the tablet surface area, (iii) the osmotic agent proportion and (iv) the drug layer polymer grade [54].

Hai Bang Lee et al (2000) studied the sandwiched osmotic tablet system (SOTS). A sandwiched osmotic tablet core surrounded by a cellulose acetate membrane with two orifices on the surfaces of both sides was successfully prepared for the purpose of delivering nifedipine. The appropriate orifice size was observed in the range of 0.50 – 1.41 mm. It was also found that the drug release rate of SOTS could be increased by incorporating hydrophilic plasticizer in the membrane, whereas it could be decreased by incorporating a hydrophobic plasticizer[55].

Sapna N et al (2003) developed a controlled porosity osmotic pump-based drug delivery system which consists of an osmotic core with the drug surrounded by a semipermeable membrane drilled with a delivery orifice, controlled porosity of the membrane is accomplished by the use of different channeling agents in the coating. The usual dose of pseudoephedrine is 60 mg to be taken three or four times daily. It has a short plasma half life of 5–8 h. Hence, pseudoephedrine was chosen as a model drug with an aim to develop a controlled release system for a period of 12 h. Sodium bicarbonate was used as the osmogent. The effect of different ratios of drug:osmogent on the in-vitro release was studied. Cellulose acetate (CA) was used as the semipermeable membrane. Different channeling agents tried were diethyl phthalate (DEP),

dibutylphthalate (DBP), dibutylsebacate (DBS) and polyethylene glycol 400 (PEG 400). It was found that drug release rate increased with the amount of osmogent due to the increased water uptake, and hence increased driving force for drug release. This could be retarded by the proper choice of channeling agent in order to achieve the desired zero order release profile. Also the lag time seen with tablets coated using diethyl phthalate as channeling agent was reduced by using a hydrophilic plasticizer like polyethylene glycol 400 in combination with diethyl phthalate. This system was found to deliver pseudoephedrine at a zero order rate for 12 h. The effect of pH on drug release was also studied[7].

Pratim K Choudhury et al (2007) developed an asymmetric membrane capsule of cellulose acetate for osmotic delivery of flurbiprofen and influence of osmogents and solubilizing agent on in vitro drug release were evaluated. Scanning electron microscopy of the membrane confirmed its porous, dense asymmetric nature. Dye test revealed in situ pore formation. The in vitro release study showed that as the proportion of osmogent and solubilizing agent was increased the release rate also increased. A good correlation was observed between the zero-order rate constant and the amount of the osmogent and solubilizing agent used[56].

Longxiao Liu et al (2008) developed the bilayer-core osmotic pump tablet (OPT) for nifedipine which does not require laser drilling to form the drug delivery orifice. The bilayer-core consisted of two layers: (a) push layer and (b) drug layer, and was made with a modified upper tablet punch, which produced an indentation at the center of the drug layer surface. Sodium chloride was used as osmotic agent, polyvinylpyrrolidone as suspending agent and croscarmellose sodium as expanding agent. The indented core tablet was coated by ethyl cellulose as semipermeable membrane containing polyethylene glycol 400 for controlling the membrane permeability. It was found that the optimal OPT was able to deliver nifedipine by an approximately zero order process up to 24 h, independent of both release media and agitation rates[57].

AK Philip et al (2008) developed an asymmetric membrane capsular system, formed in situ, for poorly water soluble drug, ketoprofen and evaluated it by both in vitro and in vivo methods for osmotic and controlled release of the drug. Membrane characterization by scanning electron microscopy showed an outer dense region

with less pores and an inner porous region for the prepared asymmetric membrane[58].

Mahalaxmi.R et al (2009) developed the extended release controlled porosity osmotic pump formulations of model drug glipizide using a wicking agent and a solubilizing agent. The effect of different formulation variables like level of wicking agent, solubilizing agent, level of pore former and membrane weight gain on in vitro release were studied. Drug release was found to be affected by the level of wicking agent and solubilizing agent in the core. Glipizide release from controlled porosity osmotic pump was directly proportional to the level of pore former (sorbitol) and inversely proportional to membrane weight gain[59].

Pramod Kumar et al (2009) developed Elementary osmotic pump (EOP) of highly water soluble drug tramadol hydrochloride (TRH). Target release profile was selected and different variables were optimized to achieve the same. Formulation variables like levels of swellable polymer (10-21.87 %) and plasticizer (0-20% w/w of polymer), and coat thickness of semipermeable membrane (SPM) were found to affect the drug release from the developed formulations. TRH release was directly proportional to the level of plasticizer and osmotic pressure generated by osmotic agent but inversely proportional to the level of swellable polymer within the core and coat thickness of SPM. Burst strength of the exhausted shells increased with increase in coat thickness but decreased with increase in level of plasticizer[60].

Mothilal M et al (2010) developed an osmotically controlled oral drug delivery system formulations of metoprolol succinate were prepared using different concentrations of mannitol, by wet granulation technique. The tablets were coated by dip coating with cellulose acetate. Stainless steel drill pins were used to make an orifice on the tablets. Orifice diameter was examined using scanning electron microscopy (SEM). With increase in osmogent content and bore size, rate of drug release were found to be increasing an optimum concentration of osmogent and bore size to give a zero order release was identified[61].

LIMITATIONS

The following limitations have contributed to the osmotic drug delivery systems[12, 13].

1. Dose dumping.
2. Rapid development of tolerance.
3. Retrieval therapy is not possible in the case of unexpected adverse event.

4. Special equipment is required for making an orifice in the system.

It may cause irritation or ulcer due release of saturated solution of drug.

MARKETED PRODUCTS

Table 2

List of Osmotic drug delivery systems in market with their dosage and use

Trade Name	Active ingredient	Design system	Dose	Use
Alpress LP	Prazosin	Push –Pull	2.5 - 5 mg	For the treatment of hypertension
Acutrim	Phenylpropanolamine	Elementary pump	75 mg	For the treatment the congestion associated with allergies, hay fever, sinus irritation, and the common cold.
Cardura XL	Doxazosin	Push –Pull	4, 8 mg	For the treatment of hypertension
Covera HS	Verapamil	Push -Pull with time delay	180, 240 mg	For the management of hypertension and angina
Ditropan XL	Oxybutinin chloride	Push –Pull	5, 10 mg	For the once daily treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency
Dynacirc CR	Isradipine	Push –Pull	5, 10 mg	For the treatment of hypertension
Invega	Paliperidone	Push –Pull	3, 6, 9 mg	For the treatment of schizophrenia
Efidac 24	Chlorpheniramine	Elementary	4 mg IR,	Chlorpheniramine is an

	Maleate	Pump	12 mg CR	antihistamine. Chlorpheniramine is used to treat sneezing; runny nose; itching, watery eyes; hives; rashes; itching; and other symptoms of allergies and the common cold.
Glucotrol XL	Glipizide	Push – Pull	5, 10 mg	For the control of hyperglycemia in patients with non-insulin-dependent diabetes
Minipress XL	Prazocine	Elementary pump	2.5, 5 mg	Antihypertensive Agents; Alphaadrenergic Blocking Agents
Procardia XL	Nifedipine	Push – Pull	30, 60, 90 mg	Calcium channel blocker. By blocking calcium, nifedipine relaxes and widens the blood vessels. It is used to treat high blood pressure and chest pain (angina).
Sudafed 24	Pseudoephedrine	Elementary pump	240 mg	Pseudoephedrine is used for the temporary relief of stuffy nose and sinus pain/pressure caused by infection (such as the common cold, flu) or other breathing illnesses (such as hay fever, allergies, bronchitis).

Volmax	Sabutamoll	Elementary pump	4, 8 mg	For relief of bronchospasm in patients with reversible obstructive airway disease.
Tegretol XR	Carbamazepine		100, 200, 400 mg	For use as an anticonvulsant drug.
Viadur	Leuprolide acetate	Implantable osmotic systems		
Chronogesic	Sufentanil	Implantable osmotic systems		Anesthetics, Intravenous; Narcotics; Adjuvants, Anesthesia; Analgesics, Opioid; Opiate Agonists
Concerta	Methylphenidate	Implantable osmotic systems	18, 27, 36, and 54 mg	A psychostimulant drug approved for treatment of attention-deficit hyperactivity disorder, Postural Orthostatic Tachycardia Syndrome, and narcolepsy.

CONCLUSION

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 advantages include precise control of zero-order or other patterned release over an extended time period—consistent release rates can be achieved irrespective of the environmental factors at the delivery site. Controlled delivery via osmotic systems also may reduce the side-effect profile by moderating the blood plasma peaks typical of conventional (e.g., instant release) dosage forms. Moreover, since efficacious plasma levels are maintained longer in osmotic

systems, avoidance of trough plasma levels over the dosing interval is possible. However, a complex manufacturing process and higher cost compared with conventional dosage forms limit their use. Although not all drugs 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, attention-deficit disorder, and other chronic disease states. Besides oral osmotic delivery systems, implants that work on osmotic principles are promising for delivery of a wide variety of molecules with a precise rate over a long period of time. Further, with the discovery of newer and potent drugs by the biotechnology industry, the need to deliver such compounds at a precise rate certainly will pave the way for osmotic delivery systems to play an increasingly important role in drug delivery.

REFERNCES

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

2. Prescott LF: The need for improved drug delivery in clinical practice, in: Prescott LF, Nimmo WS (eds), Novel Drug Delivery and Its Therapeutic Application, John Wiley, UK, **1989**: 1–11.

3. Sastry SV, De Gennaro MD, Reddy IK and Khan MA: Atenolol gastrointestinal therapeutic system Part 1: Screening of formulation variables. Drug Dev Ind Pharm 1997; 23: 2:157–165.

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

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

6. YANG Xing-Gang, ZHANG Guo-Hua, LI Wei, PENG Bo, LIU Zhi-Dong and PAN Wei-San: Design and Evaluation of

Jingzhiguanxin Monolithic Osmotic Pump Tablet. Chem Pharm Bull, 2006; 54: 4:465-469.

7. Makhija Sapna N and 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.

8. Srikonda Sastry, Kotamraj Phanidhar and Barclay Brian: Osmotic controlled drug delivery system, in Li Xiaoling, Jasti Bhaskara R (eds), Design of Controlled Release Drug Delivery Systems, McGraw-Hill Companies, INC, New York **2006**: 203-229.

9. McClelland GA, Sulton SC, Engle K and Zentner GM: The solubility–modulated osmotic pump: invitro / invivo release of diltiazem hydrochloride. Pharma Res 1991; 8:88-92.

10. Kaushal AM and Garg S: An update on osmotic drug delivery patents. Pharm Tech, Aug 2003; 27: 38-44.

11. Bhatt PP: Osmotic drug delivery systems for poorly soluble drugs. The drug delivery companies report autumn/winter 2004.

12. Parmar NS, Vyas SK and Jain NK: Advances in controlled and novel drug delivery. CBS publisher & distributors, New Delhi, pp 18-39, 2001.

13. Eckenhoff, Yum SI: The osmotic pump: novel research tool for optimizing drug regimen. Biomaterials, 1981; 2:89-97.

14. Higuchi T and Leeper HM: Improved osmotic dispenser employing magnesium sulfate and magnesium chloride. US Patent 3760804, 1973.

15. Higuchi T and Leeper HM: Osmotic dispenser with means for dispensing active agent responsive to osmotic gradient." US Patent 3995631, 1976.

16. Theeuwes F: Elementary Osmotic Pump. J. Pharm. Sci., 1975, 64, 1987-1991.

17. Kaushal AM and Garg S: An update on osmotic drug delivery patents. Pharm. Tech., 2003, 27, 38-44.

18. Good WR and Lee PI: Membrane-controlled reservoir drug delivery systems, in Langer RS, Wise DL (eds), Medical Applications of Controlled Release, I Vol., Boca Raton, CRC Press; 1984: 1–39.

19. Theeuwes F and Higuchi T: Osmotic dispensing device with maximum and

minimum sizes for the passageway. US Patent 3916899, 1975.

20. Gaebler, F: Laser drilling enables advanced drug delivery systems. Coherent article for Pharm Manufacturing, Jan 2007; 1-7.

21. Theeuwes F, Saunders RJ and Mefford WS: Process for forming outlet passageways in pills using a laser. US Patent 4088864; **1978**.

22. Liu L and Wang X: Solubility modulated monolithic osmotic pump tablet for atenolol delivery. Eur J Pharm Biopharm **2008**; 68: 2: 298-302.

23. Khanna, SC: Therapeutic system for sparingly soluble active ingredients. Ciba-Geigy Corporation, Ardsley, NY, US Patent 4992278, **1997.**

24. Zentner GM, McClelland GA and Sutton SC: Controlled porosity solubility- and resin-modulated osmotic drug delivery systems for release of diltiazem hydrochloride. J Control Release. 1991; 16: 1-2: 237–243.

25. Okimoto K, Ohike A and Ibuki R: Design and evaluation of an osmotic pump tablet (OPT) for prednisolone: a poorly water soluble drug using (SBE)7m-beta-CD. Pharm Res, 1998; 15: 10:1562-1568.

26. Theeuwes F, Swanson DR and Guittard G: Osmotic delivery systems for the beta-adrenoceptor antagonists metoprolol and oxprenolol: Design and evaluation of systems for once-daily administration. Br J Clin Pharmacol, 1985; 19: 2:69S–76S.

27. Santus G and Baker RW: Osmotic drug delivery: A review of the patent literature. J Control Release, 1995; 35: 1:1–21.

28. Eckenhoff B, Theeuwes F and Urquhart J: Osmotically actuated dosage forms for rate-controlled drug delivery. Pharm Technol 1987; 11: 96–105.

29. Jensen JL, Appel LE, Clair JH and Zentner GM: Variables that affect the mechanism of drug release from osmotic pumps coated with acrylate/methacrylate copolymer latexes. J Pharm Sci, 1995; 84: 5:530-533.

30. Vyas, S.P and Khar, R.K: Controlled drug delivery: concept and advances. Vallabh prakashan, New Delhi, pp 477-501, 2001.

31. Suresh Vyas P, Prabakaran D, Paramjit Singh, Parijat Kanaujia, Jaganathan KS, Amith Rawat: Modified push-pull osmotic

system for simultaneous delivery of Theophylline and Salbutamol: development and in vitro characterization. Int. J. Pharm. 2004; 284: 95-108.

32. Roger Rajewski A: Applicability of (SBE) 7m --CD in controlled-porosity osmotic pump tablets (OPTs). Int. J. Pharm. 2004; 286: 81-88.

33. Roger Rajewski A: Factors affecting membrane controlled drug release for an osmotic pump tablet utilizing (SBE)7m --CD as both a solubilizer and osmotic agent. J. Control. Rel. 1999; 60: 311-319.

34. Giancarlo Santus, and Richard Baker W: Osmotic drug Delivery: a review of the patent literature. J Control. Rel. 1995; 35: 1-21.

35. Kazuto Okimoto, Roger A. Rajewski, and Valentino J. Stella: Release of testosterone from an osmotic pump tablet utilizing (SBE)7m-β-cyclodextrin as both a solubilizing and an osmotic pump agent J. Control. Rel. 1999; 58: 29-38.

36. Hai Bang Lee, Longxiao Liu, Jeong Ku, Gilson Khang, Bong Lee, John M. Rhee: Nifedipine controlled delivery sandwiched osmotic tablet system. J. Control. Rel. 2000; 68: 145-156.

37. Toshiaki Nagakura, Ken Ishihara, Toshiyuki Furukawa, Kohji Masuda, Takao Tsuda: Auto-regulated Osmotic pump for insulin therapy by sensing glucose concentration without energy supply. Sensors and Actuators B. 1996; 34: 229-233.

38. Herbig SM., Cardinal J.R. and Korsmeyer K.L., Smith KL: Asymmetric-membrane tablet coatings for osmotic drug delivery. J. Control. Rel. 1995; 35: 127-136.

39. Mahalaxmi R, Phanidhar Sastri, Ravikumar, Atin Kalra, Pritam Kanagale and Narkhede. Enhancement of Dissolution of Glipizide from Controlled Porosity Osmotic Pump Using a Wicking Agent and a Solubilizing Agent. Int. J. Pharm Tech Res. 2009; 1, (3): 705-711.

40. Pradeep Vavia R and Sapna Makhija N: Controlled porosity osmotic pump-based controlled release systems of pseudoephedrine 1. Cellulose acetate as semipermeable membrane. J. Control. Rel. 2003; 89; 5-18.

41. Ji-Eon Kim, Seung-Ryul Kim, Sun-Hee Lee, Chi-Ho Lee and Dae-Duk Kim: The effect of pore formers on the controlled release of cefadroxil from a polyurethane matrix. Int. J. Pharm. 2000; 201: 29-36.

42. Sastry S, Kotamraj P and Barclay B: Osmotic controlled drug delivery system, in Li Xiaoling and Jasti Bhaskara R: Design of Controlled Release Drug Delivery Systems, McGraw-Hill Companies, INC, New York, pp 203- 229,

43. Bonsen P, Place V, Heimlich K, Kwan KC, Elementary Osmotic Pump for Indometacin. J. pharm, 2006.

44. Theeuwes F, Swanson D and Wong P: Sci., 1983; 72: 253- 258.

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

46. Haslem J and Rork GS: Controlled porosity osmotic pump." US Patent 488063, 1989.

47. Thombrea AG, Cardinall JR, DeNoto A.R, Herbig S.M and Smith K.L: Asymmetric membrane capsules for osmotic drug delivery: Development of a manufacturing process." J Cont. Rel., 1999; 57: 55-64.

48. Zentner GM, Rork GS and Himmelsteine KJ: Osmotic flow through controlled porosity films: an approach to deliver water soluble compounds." J. Cont. Rel., 1985; 2: 217-229.

49. Parmar NS, Vyas SK and Jain NK: Advances in controlled and novel drug delivery. CBS publisher & distributors, New Delhi, pp 18-39, 2001.

50. Theuwes, F, Wong PSL, Burkoth, TL, Fox DA and Bicek PR: Colonic drug absorption and metabolism. Marcel Decker, New York, 1993, pp 137-158.

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

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

53. Conley R, Gupta SK and Satyan G: Clinical spectrum of the osmotic controlled release oral delivery system (OROS): an advanced oral delivery form. Current medical research and opinion 2006; 22: 1879-1892.

54. Arora S, Ali J, Ahuja A, Baboota S and Qureshi J: Pulsatile drug delivery systems: An approach for controlled drug delivery." Ind. J. Pharm. Sci., 2006; 68(3): 295-300.

55. Malaterre V, Metz H, Ogorka J, Mader K, Gurny R and Loggia N: Influence of the hydration kinetics and the viscosity balance on the drug release performance of push-pull osmotic systems. Novartis Pharma AG, Technical R&D, Fabrikstrasse 2, CH-4056 Basel, Switzerland, 1-2.

56. Lee HB, Liu L, Ku J, Khang G, Lee B and Rhee JM: Nifedipine controlled delivery sandwiched osmotic tablet system. J Control Release, 2000; 68:145-156.

57. Choudhury PK, Ranawat MS, Pillai MK and Chauhan CS: Asymmetric membrane capsule for osmotic delivery of flurbiprofen. Acta Pharm, 2007; 57:343– 350.

58. Liu L and Xu X: Preparation of bilayer-core osmotic pump tablet by coating the indented core tablet. Int J Pham, 2008; 352: 1-2:225-230.

59. Philip AK and Pathak K: *In situ* formed phase transited drug delivery system of ketoprofen for achieving osmotic controlled and level a in vitro in vivo correlation. Ind J pharm Sci, 2008; 70: 6:745-753.

60. Mahalaxmi R, Sastri P, kumar R, Kalra A, Kanagale P and Narkhede: Enhancement of Dissolution of Glipizide from Controlled Porosity Osmotic Pump Using a Wicking Agent and a Solubilizing Agent. Int J PharmTech Res, 2009; 1: 3:705-711.

61. Kumar Pramod, Singh Sanjay and Mishra Brahmeshwar: Development and Evaluation of Elementary Osmotic Pump of Highly Water Soluble Drug: Tramadol Hydrochloride. Current Drug Delivery, 2009; 6:130-139.

62. Mothilal M, Damodharan N, Lakshmi KS, Sharanya VB and Srikrishna T: Formulation and *invitro* evaluation of osmotic drug delivery system of metoprolol succinate. Int J Pharm Pharm Sci, 2010; 2: 2:64-68.