JPRHC

Review Article

CONTROLLED-POROSITY OSMOTIC PUMP TABLETS-AN OVERVIEW

CH. AJAY BABU[1], M. PRASADA RAO[2] AND *VIJAYA RATNA J.[1]

For author affiliations, see end of text

This paper is available online at www.jprhc.com

ABSTRACT

Conventional drug delivery systems have little control over their drug release and almost no control over the effective concentration at the target site. This kind of 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 process of osmosis. 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. semipermeable 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 and the basic components of controlled porosity osmotic pump tablets have been discussed briefly.

Keywords: Osmotic pump, controlled-porosity osmotic pump tablet, semipermeable membrane, osmogent, leachable pore formers.

INTRODUCTION

Osmotically Controlled Drug Delivery System (OCDDS)

Osmotic devices are the most reliable controlled drug delivery systems (CDDS) and can be employed as oral drug delivery systems. Osmotic pressure is used as the driving force for these systems to release the drug in a controlled manner. Osmotic pump tablet (OPT) generally consists of a core including the drug, an osmotic agent, other excipients and semipermeable membrane coat [1]. The design, mechanism and uses of various types of osmotic systems are shown in table 1 [2]. In this study mainly the basic components of controlled porosity osmotic pump tablets have been discussed.

Advantages

- Easy to formulate and simple in operation.
- Improve patient compliance with reduced frequency.
- Prolonged therapeutic effect with uniform blood concentration.

Disadvantages

- Dose dumping
- Rapid development of tolerance
- Retrieval therapy is not possible in the case of unexpected adverse events

Types of Osmotically controlled drug delivery systems:

- Elementary osmotic pump
- Multi chambered osmotic pumps
- Push-pull osmotic pumps
- Osmotic pumps with non-expanding second chamber
- **Miscellaneous types**
- Controlled-porosity osmotic pumps
- Modified osmotic pumps for insoluble drugs
- Multi particulate delayed release systems
- Monolithic osmotic pumps

Table 1. Different types of osmotic systems-Design, mechanism and uses

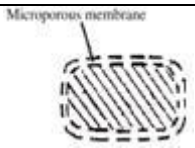
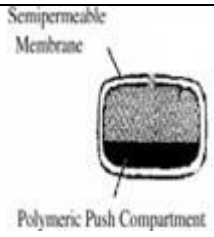
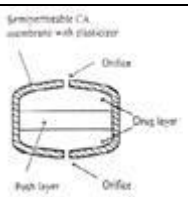
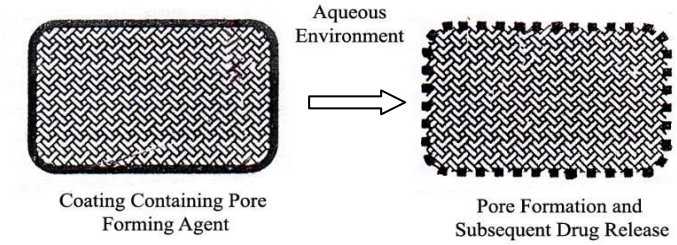
Osmotic System	Design of Dosage Form	Mechanism	Applications	Figures
Single chamber osmotic pumps				
Elementary Osmotic Pump (EOP)	**Core:** API ± osmogents **Coat:** Semi permeable membrane with delivery orifice	The water penetrates inside the dosage form. This results in formation of saturated solution of drug within the core, which is dispensed at a controlled rate from the delivery orifice present in the membrane.	**Moderately soluble** API 60- 80% constant release	
Controlled-porosity osmotic pump (CPOP)	**Core:** API ± osmogents **Coat:** Semi permeable membrane containing water soluble additives	Delivery orifice is formed by the incorporation of a leachable component. Once the tablet comes in contact with aqueous environment, Water-soluble additives dissolve lead to the formation of a microporous membrane. Water diffuses into the core through the microporous membrane, creating an osmotic gradient and thereby controlling the release of drug.	Poorly soluble drugs	
Multi-chamber osmotic pumps				
Push-pull osmotic pump (PPOP)	**Core Tablet:** Layer 1: API ± osmogents Layer 2: Polymeric osmotic agents **Coat:** Semi permeable membrane with delivery orifice	After coming in contact with the aqueous environment, polymeric osmotic layer swells and pushes the drug layer, and thus releasing drug in the form of fine dispersion through the orifice.	For delivery of APIs having **extremes of water solubility** Modifications can be done: - delayed push-pull - multi-layer push- pull - push-stick system	
Sandwiched Osmotic tablets (SOTS)	**Core tablet:** 3 layers Middle layer: push layer 2 attached layers: API **Coat:** Semi permeable membrane with **two side** delivery orifice	The middle push layer swells and drug is released from delivery orifices present on two sides of the tablet.	API release from **two sides** of tablets.	

Table.2 Osmotic pressures of saturated solution of commonly used osmogents [15]

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. $12H_2O$	36
Sodium phosphate dibasic. 7 H_2O	31
Sodium phosphate dibasic. 12 H_2O	31
Sodium phosphate monobasic. H_2O	28
Sodium phosphate dibasic. Anhydrous	21

Figure 1: CPOP tablet before and after dissolution studies



Controlled-Porosity Osmotic Pump (CPOP)

The controlled-porosity osmotic pump tablet concept was developed as an oral drug delivery system by Zentner *et al* (1985, 1991), Zentner and Rork (1990), Appel and Zentner (1991), and Mc Celland *et al*. (1991). The controlled-porosity osmotic pump tablet (CPOP) is a spray-coated or coated tablet with a semipermeable membrane (SPM) containing leachable pore forming agents. They do not have any aperture to release the drugs; drug release is achieved through the pores, which are formed in the semipermeable wall *in situ* during the operation. In this system, the drug, after dissolution inside the core, is released from the osmotic pump tablet by hydrostatic pressure and diffusion through pores created by the dissolution of pore formers incorporated in the membrane (Fig. 1). The hydrostatic pressure is created either by an osmotic agent or by the drug itself or by a tablet component, after water is imbibed across the semipermeable membrane.

This membrane after formation of pores becomes permeable for both water and solutes. A controlled-porosity osmotic wall can be described as having a sponge like appearance. The pores can be continuous that have micro porous lamina, interconnected through tortuous paths of regular and irregular shapes. Generally, materials (in a concentration range of 5% to 95%) producing pores with a pore size from 10 Å -100 μm can be used [3].

This system is generally applicable for only water-soluble drugs as poorly water soluble drugs cannot dissolve adequately in the volume of water drawn into the OPT. Recently this problem was overcome by adding agents like sulfobutyl ether-β-cyclodextrin $(SBE)_{7m}$-β-CD or hydroxypropyl-β-cyclodextrin (HP-β-CD) as solubilizing and osmotic agents. Several approaches have been developed to prepare the porous membrane by spray coating using polymer solutions containing dissolved or suspended water-soluble materials. The rate of drug release can also be varied by having different amounts of osmogents in the system to form different concentrations of channeling agents for delivery of the drug from the device. Incorporation of the cyclodextrin-drug complex has also been used as an approach for the delivery of poorly water-soluble drugs from the osmotic systems, especially controlled-porosity osmotic pump tablets [4].

Advantages

1. The OPT can be so designed that delivery of its drug would follow zero order kinetics and thus better control over the drug's *in vivo* performance is possible.
2. The drug release from the osmotically controlled drug delivery systems are independent of the gastric pH and hydrodynamic conditions, which is mainly attributed to the unique properties of the SPM employed in the coating of osmotic formulations.

3. The delivery rate of drug from these systems is highly predictable and can be programmed by modulating the terms.

4. It is possible to attain better release rates than those obtained with conventional diffusion based drug delivery systems.
5. Drug release from the OCODDSs exhibits significant *in vitro-in vivo* correlation [*IVIVC*] within specific limits [2].

Disadvantages

1. Drug release from the osmotic systems is affected to some extent by the presence of food.
2. Retrieval of therapy is not possible in the case of unexpected adverse events.

Basic components required for controlled-porosity osmotic pump

a) Drug
b) Osmotic agent
c) Semipermeable membrane
d) Channeling agents or pore forming agents.

a. Criteria for selection of a drug:

- Short biological Half-life (2- 6 hrs)
- High potency
- Required for prolonged treatment (e.g: Nifedipine, Glipizide, Verapamil and 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 [3].

Roger A. Rajewski *et al* (2004) investigated the application of controlled-porosity osmotic pump tablet (OPT) utilizing $(SBE)_{7m}$ -β-CD both as a solubilizer and an osmotic agent for drugs with varying physical properties. OPTs utilizing $(SBE)_{7m}$ -β-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 $(SBE)_{7m}$ -β-CD acts primarily as an osmotic and an OPT control agent. Significantly, $(SBE)_{7m}$ -β-CD not only enhances the delivery of poorly soluble drugs from OPTs but acts as a controlling excipient for soluble drugs such that the release rate, corrected for tablet surface area, of both poorly soluble and soluble drugs are similar [4].

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-β-cyclodextrin, $(SBE)_{7m}$ -β-CD, both as solubilizing agent and osmotic agent. The release rate of chlorpromazine (CLP) from OPTs containing $(SBE)_{7m}$ -β-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 [5].

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 2). These osmotic pressures can produce high water flows across semipermeable membranes [3]. The osmotic water flow across a membrane is given by the equation,

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

Where dv/dt, is the rate of water flow across the membrane of area A, thickness *l*, permeability θ in $cm^3.cm/cm^2$. h. atm, and Δ π [6].

Stella J. *et al* (1999) developed controlled-porosity osmotic pump system for poorly water-soluble drugs such as testosterone using sulfobutyl ether β-cyclodextrin $(SBE)7_m$-β-CD sodium salt, which can act as both a solublizing agent and an osmotic agent. The effect of $(SBE)_{7m}$-β-CD as the solubilizing and osmotic pump agent was compared with hydroxypropyl-β-cyclodextrin (HP-β-CD), a

neutral cyclodextrin, and a sugar mixture (osmotic agent only). Testosterone release from the device was significantly faster with $(SBE)_{7m}$-β-CD than with HP-β-CD or the sugar mixture. It was concluded that $(SBE)7_m$-β-CD provides novel properties for the development of controlled porosity osmotic pump tablet for poorly soluble drugs.[7]

Table 3. Specifications for controlled- porosity osmotic pump [15]

Materials	Specifications
Plasticizers and flux Regulating agents	0 to 50, preferably 0.001 to 50 parts per 100 parts of wall material
Surfactants	0 to 40, preferably 0.001to 40 parts per 100 parts of wall material
Wall thickness	1 to 1000, preferably 20 to 500 m
Microporous nature Pore forming additives	5 to 95% pores between 10a to 100 m diameter 0.1 to 60%, preferably 0.1 to 50%, by weight, based on the total weight of additive and polymer

Table 4. Specifications for core of controlled- porosity osmotic pump [15]

Property	Specifications
Core loading (size)	0.05 mg to 5 g or more (include dosage forms for Humans and animals)
Osmotic pressure developed by a solution of core	8 to 500atm typically, with commonly encountered water soluble drugs and excipients.
Core solubility	To get continuous, uniform release of 90% or greater of the initially loaded core mass solubility, S, to the core mass density,ρ, that is S/ρ, must be 0.1 or lower. Typically it occurs when 10% of the initially loaded core mass saturates a volume of external fluid equal to the total volume of the initial core mass.

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 [8].

Ideal properties of semipermeable membrane [9]

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 the 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 rates can be used to estimate water flux rates.
c) The reflection coefficient (σ) or "leakiness" of the osmotic agents should approach the limiting value of unity. But polymer membranes 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 [8].

Toshiaki Nagakura *et al* (1996) designed an osmotic pump using a semipermeable membrane that changes its volume according to the concentration of the outside solution. By a mechanochemical actuator mechanism, an insulin pump works by changing the glucose concentration. It was found that this pump may possibly be used in the treatment of diabetes mellitus patients [10].

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 permeability of the coating to water can be adjusted by controlling the membrane structure, thereby allowing the control of the release kinetics without altering the coating material or significantly varying its concentration. 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 [11].

d. Channeling agents/ 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, D -mannitol, bovine serum albumin (BSA), diethylphthalate, dibutylphthalate and sorbitol [12, 13, 14].

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 [12].

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 [13].

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 D -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%) [14].

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. Release was insensitive to the pH and degree of agitation in the receptor media. The concept of osmotically actuated drug delivery on an equivalent mass per unit surface area basis was demonstrated [15].

Rajan K. Verma *et al* (2002) studied the formulation aspects in the development of osmotically controlled oral drug delivery systems. In this review, different types of oral osmotic systems, various factors governing drug release from these systems and critical formulation factors were discussed [16].

Gaylen. M *et al* (1991) studied the application of either solubility or resin-modulated method to effectively manipulate drug release kinetics from controlled porosity osmotic pumps. These solubility-modulated devices administered to dogs release diltiazem hydrochloride with similar *in vivo / in vitro* kinetics. These approaches may be applicable to extend osmotic pump technology to drugs with intrinsic water solubility that is too high or low for conventional osmotic pump formulation [17].

Sanjay Garg *et al* (2003) studied the development and evaluation of extended release formulations of isosorbide mono nitrate (IMN) based on osmotic technology. The release from developed formulations was independent of pH and agitational intensity, but dependent on the osmotic pressure of the release media. Results of SEM studies showed the formation of pores in the membrane from where the drug release occurred. Prediction of steady state levels, showed the plasma concentrations of IMN to be within the desired range [18].

Andrew Tasker *et al* (2000) studied the use of osmotic mini pumps as alternatives for injections for sustained drug delivery in adult rats. Sustained delivery rat pumps were assigned to control, mini-pump or sham surgery treatment. Based on the results the use of osmotic mini-pumps is a viable alternative to repeated injections for sustained delivery [19].

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 [20].

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. The indented tablets were coated by using a conventional pan-coating process. 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

Table 5. Patents related to Controlled porosity osmotic pump

S.No.	U.S. Patent number	Type of osmotic system
1.	4,968,507	CONTROLLED POROSITY OSMOTIC PUMP*
2.	4,880,631	Controlled-porosity osmotic pump of Diltiazem L-maleate*
3.	4,256,108	Microporous semipermeable laminated osmotic system
4.	4,160,452	Osmotic system having laminated wall comprising of semipermeable lamina and microporous lamina
5.	4,340,054	Semipermeable membrane consisting of impregnated microporous membrane
6.	4,450,198	Semipermeable membrane consisting of a microporous film impregnated with a hydrophilic polymer
7.	4,946,686	Controlled-porosity solubility modulated osmotic pump for delivering of drug having low water solubility*
8.	4,994,273	Controlled-porosity solubility modulated osmotic pump for delivering of drug having low water solubility

Table 6. Marketed products of different osmotic systems

Product Name	Active	Design	Dose
Acutrim	Phenylpropanolamine	Elementary pump	75 mg
Alpress LP	Prazosin	Push -Pull	2.5 - 5 mg
Cardura XL	Doxazosin	Push -Pull	4, 8 mg
Covera HS	Verapamil	Push -Pull with time delay	180, 240 mg
Ditropan XL	Oxybutinin chloride	Push -Pull	5, 10 mg
Dynacirc CR	Isradipine	Push -Pull	5, 10 mg
Efidac 24	Pseudoephiderine	Elementary Pump	60 mg IR, 180 mg CR
Efidac 24	Chlorpheniramine meleate	Elementary Pump	4 mg IR, 12 mg CR
Glucotrol XL	Glipizide	Push - Pull	5, 10 mg

permeability. The *in- vitro* drug release profiles of various formulations were evaluated by similarity factor (f_2). 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[21]. Different types of osmotic systems-design, mechanism and uses and the specifications for the core of controlled porosity osmotic pump tablet and various marketed products of different osmotic systems are shown in Tables 3, 4, 5 & 6.

CONCLUSIONS

It can be concluded that the oral controlled-porosity osmotic pump system comprising a monolithic tablet coated with a semipermeable membrane containing different levels of pore forming agents can be developed for poorly water soluble drugs. These osmotic devices could be designed and optimized to deliver poorly soluble drugs at a controlled rate for extended periods of time by changing the drug: osmogent ratio, type of channeling agent and its concentration. The rate of release may be controlled through: 1) the level of pore formers incorporated into the wall; 2) the nature of the insoluble polymer component of the wall; 3) the thickness of the surface of the wall; 4) total solubility and osmotic pressure of the core; and 5) the drug load in the core. The osmotic system may be used to deliver drugs at a controlled rate over a period of 12 hours. This system is simple to prepare with no drilling required and hence it can be used in the field of controlled delivery of drugs.

REFERNCES

1. Aulton M. E. Pharmaceutics The Science of Dosage form Design. Churchill Livingstone Press Elsevier. Third edition, 2007; pp.461.
2. M. C. Gohel, Parikh .R.K, Shah. N.Y. Osmotic Drug Delivery: An Update. Pharma info.net. 2009; 7: 2.
3. Suresh Vyas P., Prabakaran D., Paramjit Singh, Parijat Kanaujia, Jaganathan K.S., 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.
4. Roger Rajewski A., *et al.* Applicability of $(SBE)_{7m}$ -β-CD in controlled-porosity osmotic pump tablets (OPTs). Int. J. Pharm. 2004; 286: 81-88.
5. Roger Rajewski A., *et al*. Factors affecting membrane controlled drug release for an osmotic pump tablet utilizing $(SBE)_{7m}$ -β-CD as both a solubilizer and osmotic agent. J. Control. Rel. 1999; 60: 311-319.
6. Giancarlo Santus, Richard Baker W. Osmotic drug Delivery: a review of the patent literature. J Control. Rel. 1995; 35: 1-21.
7. 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.
8. 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.
9. Shailesh Sharma. Osmotic controlled drug delivery. Pharmainfo.net. 2008; 6(3).
10. 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.
11. Herbig S.M., Cardinal J.R., Korsmeyer K.L., Smith K.L. Asymmetric-membrane tablet coatings for osmotic drug delivery. J. Control. Rel. 1995; 35: 127-136.
12. Mahalaxmi.R, Phanidhar Sastri1, Ravikumar, Atin Kalra, Pritam Kanagale, 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.
13. Pradeep Vavia R., 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.
14. 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.
15. Gaylen Zentner M., Gerald S. Rork and Kenneth J. Himmerstein. THE CONTROLLED POROSITY OSMOTIC PUMP. J. Control. Rel. 1985; 1: 269-282.
16. Rajan Verma K., Kivi Murali Krishna, Sanjay Garg. Formulation aspects in the development of Osmotically Controlled Oral Drug Delivery Systems (OCODDs). J. Control. Rel. 2002; 79: 7-27.
17. Gaylen Zentner M., Gregory McCelland A., Steven Sutton C. Controlled porosity solubility and resin-modulated osmotic drug delivery systems for release of Diltiazem hydrochloride. J. Control. Rel. 1991; 16: 237-244.
18. Sanjay Garg, Rajan Verma k., Aditya Kaushal M. Development and evaluation of extended release formulations of Isosorbide mononitrate based on osmotic technology. Int. J. Pharm. 2003; 263: 9-24.
19. Andrew Tasker R., Tracy Doucette A., Catherine Ryan L. Use of osmotic minipumps for sustained drug delivery in rat pups: effects on physical and Neurobehavioral Development. Physiology & Behaviour. 2000; 71: 207-212.
20. AK Philip, Kamla Patha. *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.
21. Longxiao Liu, Xiangning Xu. Preparation of bilayer-core osmotic pump tablet by coating the indented core tablet. Int. J.

Pham. 2008; 352, (1-2): 225-230.
22. Hsiu-O Ho, Ying-Ku Lin. Investigations on the drug releasing mechanism from an Asymmetric membrane-coated capsule with an *in situ* formed delivery orifice. J. Control. Rel. 2003; 89: 57-69.
23. Ming-Thau Sheu, Chun-Yu Wang, Hsiu-O Ho, Ling-Hong Lin, Ying-Ku Lin. Asymmetric membrane capsules for delivery of poorly water-soluble drugs by osmotic effects. Int. J. Pharm. 2005; 297: 89-97.

AUTHORS ADDRESSES AND AFFILIATIONS:

1. A.U College of Pharmaceutical Sciences,
Andhra University, Visakhapatnam, -530 003(A.P), India

2. M.A.M. College of pharmacy,
Kesanupalli, Narasaraopet, Guntur (Dist.) -522601(A.P), India

Address for Communication:

Prof. J Vijaya Ratna, M.Pharm., P.h D., PGDAS
A.U College of Pharmaceutical Sciences
Andhra University
Visakhapatnam-530003
Andhra Pradesh
India.
E-mail: vijaya.ratna@gmail.com
Phone No.: +91-891-2844940 (O) +91-891-2754446 (R)