REVIEW ARTICLE

A Review on Controlled Porosity Osmotic Pump Tablets

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ABSTRACT

Osmotically controlled drug delivery systems have a major role in the drug delivery technology. In that the oral controlled porosity osmotic pump tablets have very effective impact. The drug delivery though this type of formulation is independent of the physiological parameters of the body and also the rate drug release can be made in controlled manner. The formulation techniques are simple and reliable. The present study focuses on the importance, past and present status and formulation challenges of this type of drug delivery system.

KEYWORDS

INTRODUCTION

Oral Controlled Release Drug Delivery Systems

The oral drug delivery systems are most widely using technique in administration of drugs. In that tablets are the most preferred formulation by the patients. In case of long term treatment of chronic disease conditions conventional tablets are required to be administered in multiple doses therefore it have several disadvantages.[1] In this case the controlled release tablet formulations are preferred because they offer good patient compliance, maintain uniform therapeutic drug level, reduce dose and side effects and increase the safety margin for high potency drugs.[2]

Oral controlled release drug delivery system is an oral delivery system that provides continuous release of drugs with predictable and reproducible kinetics for a predetermined period, either throughout the course of GI transit or by targeting the delivery of a drug near/in a specific region within the GI tract for either a local or systemic action.[1]
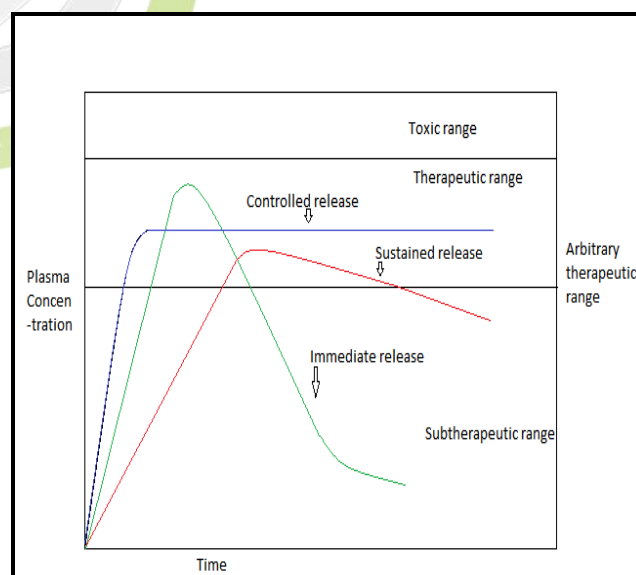

Figure 1: Drug release profile showing differences between controlled release, sustained release and immediate release dosage forms.[3]

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Advantages of Controlled Drug Delivery Systems

1. Patient compliance due to reduction in the frequency of dosing.
2. Employ minimum drug.
3. Minimize or eliminates local and systemic side effects.
4. Obtain less deduction in drug activity with chronic use.
5. Minimize drug accumulation with chronic dosing.
6. Improves efficacy in treatment.
7. Cure or control confirm more promptly.
8. Improve control of condition i.e. reduce fluctuation in drug level.
9. Improve bioavailability of same drugs.
10. Make use of special effects, e.g. sustained release aspect for morning relief of arthritis by dosing before bedtime.[3]

Classification of Controlled Drug Delivery Systems

Diffusion Controlled

➢ Reservoir devices
➢ Matrix devices
➢ Reservoir and monolithic

Dissolution Controlled

➢ Encapsulation
➢ Matrix

Water Penetration Controlled

➢ Osmotically controlled
➢ Swelling controlled

Chemically Controlled

➢ Erodible systems
➢ Drug covalently linked with polymer

Hydrogels

➢ Chemically controlled
➢ Swelling controlled

➢ Diffusion controlled
➢ Environment responsive

Ion-Exchange Resins

➢ Cationic exchange
➢ Anionic exchange[3]

Osmotically Controlled Drug Delivery Systems

Osmosis

Osmosis is the process of movement of solvent molecules from lower solute concentration to higher concentration through a semi permeable membrane. Osmosis is the phenomenon that makes controlled drug delivery, a reality. Osmotic pressure created due to imbibition of fluid from external environment into the dosage form regulates the delivery of drug from the osmotic device.

Rate of drug delivery from osmotic pump is directly proportional to the osmotic pressure developed due to imbibition of fluids by osmogent. Osmotic pressure is a colligative property of a solution in which the magnitude of osmotic pressure of the 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 the solute (osmogent).[4,5]

Principles of Osmosis

The first report of an osmotic effect dates to 1748 (Abbenollet). But obtained the first quantitative measurement was obtained by Pfeffer in 1877. In Pfeffer experiment, a membrane permeable to water but impermeable to sugar was 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 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.

$$\pi = \Phi\, c\, r\, t$$

Where Φ is the osmotic coefficient of the solution, 'c' is the molar concentration of sugar in the solution, 'r' is the gas constant and 't' is the absolute temperature.

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 semi permeable 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' is water flow across the membrane of area 'A', thickness 'L', and the permeability 'Q' in cm^2 and $\Delta\pi$ is the osmotic pressure difference between the two solutions on either side of the membrane. This equation is strictly for completely selective membrane that is membrane permeable to water but completely impermeable to osmotic agent.[4,5]

Types of Osmotic Drug Delivery Devices

They fall in two categories

Implantable

- The Rose and Nelson Pump
- Higuchi Leeper Pump
- Higuchi Theuwes pump
- Implantable Miniosmotic pump
- Alzet osmotic pumps

Oral osmotic Pump

Single chamber osmotic pump

- Elementary osmotic pump

Multi chamber osmotic pump

- Push pull osmotic pump
- Osmotic pump with non-expanding second chamber

Specific Types

- Controlled porosity osmotic pump
- Osmotic bursting osmotic pump
- Liquid OROS

Delayed Delivery Osmotic Device

- Telescopic capsule
- Oros CT (colon targeting)
- Sandwiched oral therapeutic system
- Osmotic pump for insoluble drugs
- Monolithic osmotic systems
- Osmat

Controlled Porosity Osmotic Pumps

The pump can be made with single or multi-compartment dosage form, in either form, the delivery system comprises a core with the drug surrounded by a membrane which has an asymmetric structure, i.e. comprises a thin dense skin layer supported by a porous substructure. The membrane is formed by phase inversion process controlled by the evaporation of a mixed solvent system. Membrane is permeable to water but impermeable to solute and insensitive pore forming additive dispersed throughout the wall.

When exposed to water, low levels of water-soluble additive are leached from polymer materials that were permeable to water yet remained insoluble. Then resulting sponge like structure formed the controlled porosity walls of interest and was substantially permeable to both water and dissolved drug agents.

Rate of drug delivery depends upon the factors water permeability of the semi permeable membrane and the osmotic pressure of the core formulation, thickness and total surface area of coating. All of these variable are under the control of the designer and do not vary under physiological condition. The rate of flow 'dv/dt' of water into the device can be represented as

$$dv / dt = Ak / h\ (Dp\text{-}DR)$$

Where   k = Membrane permeability, A   = Area of the membrane

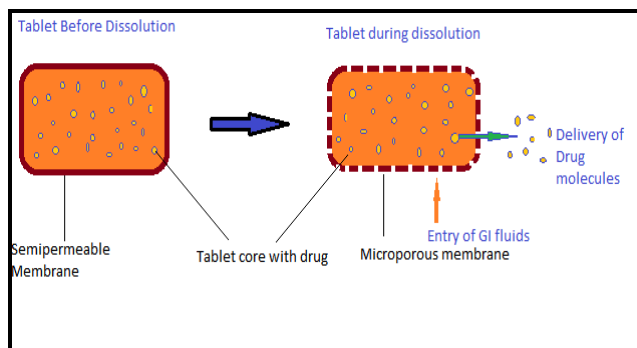Dp = Osmotic pressure difference, DR = Hydrostatic pressure difference

Figure 2: Drug release from controlled porosity osmotic pump tablets

Advantages

1. They typically give a zero order release profile after an initial lag.

2. Deliveries may be delayed or pulsed if desired.

3. Drug release is independent of gastric pH and hydrodynamic condition.

4. The release mechanisms are not dependent on drug.

5. A high degree of *in vitro* and *in vivo* correlation

6. The rationale for this approach is that the presence of water in G.I.T is relatively constant, at least in terms of the amount required for activation and controlling osmotically base technologies.[4,5,6]

Basic Components of Osmotic Systems

Drug

Drugs which have short biological half-lives and which are used for prolonged treatment are ideal candidates for osmotic systems. Various drug candidates such as Diltiazem HCl, Carbamazepine, Metoprolol, Oxprenolol, Nifedipine, Glipizide, etc are formulated as osmotic delivery.

Osmotic Agent

Osmotic components usually are ionic compounds consisting of either inorganic salts or hydrophilic polymers. Different magnesium chloride or sulfate; 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, sodium citrate, sodium ascorbate; carbohydrates like mannose, sucrose, etc.

Semipermeable Membrane (SPM)

An important part of the osmotic drug delivery system is the SPM housing. Therefore, the polymeric membrane selection is key to osmotic delivery formulation. The membrane must possess certain performance criteria such as:

- Sufficient wet strength and water permeability

- Should be biocompatible

- Rigid and non-swelling

- Should be sufficiently thick to withstand the pressure within the device.

Example: Cellulose esters like cellulose acetate, cellulose acetate butyrate, cellulose triacetate and ethyl cellulose and eudragits.

Plasticizers

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. Example: Polyethylene glycols, castor oil.[4,5]

Factors Affecting Drug Release Rate

Solubility

Active pharmaceutical ingredients for osmotic delivery should have water solubility in the desired range to get optimized drug release. However, by modulating the solubility of these drugs within the core, effective release patterns may be obtained for the drugs, which might otherwise appear to be poor candidates for osmotic delivery.

Osmotic Pressure

The next release controlling factor that must be optimized is the osmotic pressure gradient

between inside the compartment and the external environment. The simplest and most predictable way to achieve a constant osmotic pressure is to maintain a saturated solution of osmotic agent in the compartment.

Table 1: Various important osmotic agents and their osmotic pressure

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

Size of Delivery Orifice

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 build up in the system. Methods to create a delivery orifice in the osmotic tablet coating are mechanical drill, laser drill, and use of leachable substances in the semipermeable coating.[7]

Coating Membrane

Release rate affected by the type and nature of membrane forming polymer, thickness of the membrane, and presence of other additives (type and nature of plasticizer, flux additives, etc.). Membrane permeability can be increased or decreased by proper choice of membrane-forming polymers and other additives.[6]

Evaluation of Porous Osmotic Pump Tablets

Drug - Excipient Compatibility Studies

1. Fourier transform infrared (FT-IR) spectroscopy

2. Differential scanning calorimetry (DSC)

Powder Flow Properties

a) Angle of repose

b) Bulk density

c) Porosity

d) Carr's index

Physicochemical Parameters

a) Diameter

b) Thickness

c) Hardness

d) Friability

e) Weight uniformity

f) Determination of drug content

In vitro Drug Release Studies Porous Osmotic Pump Tablets

Kinetics Modeling of Drug Dissolution Profiles

a) Zero order release kinetic

b) First order release kinetic

c) Higuchi release model

d) Koresmeyer and Peppas kinetics

Optimization

Effect of pH on drug release

Effect of agitation intensity on drug release

Effect of Osmotic Pressure

Membrane morphology of porous osmotic pump tablet

Stability Studies

Review Literature

Makhija SN et al studied about controlled porosity osmotic pump-based drug delivery system of pseudoephedrine. 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 semi permeable membrane. The effect of polymer loading on *in vitro* drug release was studied. 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. The effect of pH on drug release was also studied.[8]

Chauhan CS et al formulated the asymmetric membrane-controlled porosity osmotic pumps of cellulose acetate with different pore forming agents such as glycerol, polyethylene glycol and dibutyl phthalate, were fabricated and studied for osmotic release behavior from the system. The effect of pore forming agents on the porosity of asymmetric membrane was characterized by scanning electron microscopy, and also by void volumes determination of each membrane. No significant effect on the thickness and weight variation of asymmetric membrane capsule were observed, but the tensile strength of the film varied with the concentration and type of pore forming agent used.[9]

Yueqi BI et al developed controlled porosity of osmotic pump system with biphasic release of Theophylline. The developed system was composed of a tablet-in-tablet (TNT) core and a controlled porosity coating membrane**.** Micro-environmental osmotic pressure decreased and micro-environmental pH increased continuously during the whole dissolution process, theophylline release was dominated by the successive dissolution of sodium chloride and sodium phosphate.[10]

Kanagale P et al developed a porous osmotic pump–based controlled release system of Oxybutynin. The effect of different formulation variables, namely, ratio of drug to osmogent, membrane weight gain, and level of pore former on the *in vitro* release of oxybutynin was studied. It was found that drug release rate increased with the amount of osmogent. Oxybutynin release was inversely proportional to the membrane weight gain; however, directly related to the level of pore former, sorbitol, in the membrane. This system was found to deliver oxybutynin at a zero order rate for 20 h.[11]

Kazuto O et al formulated a controlled-porosity osmotic pump tablet (OPT) utilizing (SBE)7m-CD as both a solubilizer and an osmotic agent for drugs with varying physical properties. An appropriate composition ratio of (SBE)7m-CD to drug at which drug release from the OPT was complete and pH-independent within the physiological pH range of the GI tract was determined for each drug. The results confirmed that (SBE)7m-CD serves as both a solubility modulator and as an osmotic pumping agent for OPTs, from which the release rate of both water-soluble and poorly water-soluble drugs can be controlled.[12]

Chauhan CS et al studied the release mechanism of drug having low water solubility by means of controlled porosity osmotic pump. The capsule membrane was prepared by phase inversion technique. The drug selected for this study, flurbiprofen, has low water solubility and hence is unable to create osmotic pressure to cause drug release. To enhance the solubility and its osmotic pressure, this study was conducted with a solubility enhancer sodium lauryl sulphate (SLS). The release rate increased as the concentration of pore forming agent and presence of solubility enhancer.[13]

Wen-Jen L et al developed a microporous-controlled delivery system for theophylline via coating a blend of PCL and PEG on the surface of tablet. The release rate of coated tablets was increased by increasing the amount of pore-

forming agent, and the corresponding values from tablets coated in dichloromethane were less than in acetone. The release of drug from tablets coated in acetone showed a profile more close to a zero order constant release profile.[14]

Nurten O et al investigated on the effect of the delivery orifices and the concentration of osmotic agents on the rate of release of Ibuprofen. Ibuprofen tablets were prepared and sodium chloride and polyethylene glycol 6000 were used as osmotic agents. The tablets were coated with a mixture of cellulose acetate and polyethylene glycol 400 by the use of a modified fluidized bed apparatus. It was observed that the release rate of ibuprofen was influenced by the concentration of osmotic agents sodium chloride and polyethylene glycol 6000.[15]

Prakash RB et al developed swellable controlled porosity osmotic pump tablet of theophylline and to define the formulation and process variables responsible for drug release by applying statistical optimization technique. Formulations were prepared based on Taguchi orthogonal array design and fraction factorial design for core and coating, respectively. The results confirmed that the factors responsible for drug release were osmotic agents (core) and pore former (membrane).[16]

Zulfequar AK et al formulated enteric coated microporous osmotic pump tablet to prolong the drug release of an antipsychotic drug, quetiapine fumarate. The effect of formulation variables such as concentration of sodium chloride, types of pore former (PEG 400, PEG 4000 and PEG 6000), coat thickness (100 and 200 μm) of microporous membrane were evaluated for drug release characteristics. A zero order release was obtained and the formulations were found to be stable up to 3 months when tested for stability at 40OC/75% RH.[17]

Rajagopal K designed a Controlled porosity osmotic pump tablet (CPOP) system to deliver Nifedipine (NP) and Metoprolol (MP) in a controlled manner up to 12 h. It was prepared by incorporating drugs in the core and coated with various types (PVP, PEG-400 and HPMC) and

levels (30, 40 and 50% w/w of polymer) of pore former at a weight gain of 8, 12 & 15%. The developed osmotic system is effective in the multi-drug therapy of hypertension by delivering both drugs in a controlled manner.[18]

Ahmed AE prepared Etodolac controlled porosity osmotic pump tablets by using osmogent type (sodium chloride, potassium chloride, mannitol, and fructose), drug/osmogent ratio (1:0.25, 1:0.50, and 1:0.75), weight gain percentage (1–5%, w/w), and pore former concentration (5%, 10%, and 20%, v/v) etc. Statistical analysis and kinetic modeling of drug release data were estimated. When compared to the commercial immediate-release Napilac® capsules, the optimum CPOP tablets (F4–34) provided enhanced bioavailability and extended duration of effective Etodolac plasma concentration with minimum expected potential for side effects in healthy volunteers.[19]

Krunal M.U et al formulated Controlled porosity osmotic pump tablets of Methylphenidate HCl. Mannitol was used as an osmotic agent and cellulose acetate (CA) was used as semipermeable membrane. Polyethylene glycol 400(PEG-400) was employed as a pore forming agent. Effect of varying concentration of pore former and osmogen was also evaluated. The observed result revels that osmotic agent and pore former have significant effect on drug release up to 12hr in successful development of micro porous osmotic pump tablets containing Methylphenidate Hydrochloride using mannitol and PEG400 as key excipients.[20]

Sanjay M et al prepared Controlled porosity osmotic pump tablets of Milnacipran hydrochloride by using PEG 8000 as pore former. Formulation designed by 2^3 factorial designs. The effect of pH and agitation on drug release was carried out. DSC for drug excipient compatibility and SEM for microporous structure of coating membrane were performed. The drug release was directly proportional to amount of osmogent, concentration o poreformer and inversely proportional to membrane weight gain.[21]

Fatima SD et al designed Controlled porosity osmotic pump tablets of ketorolac using poreformer (PVP), plasticizer (dibutyl phthalate). It was confirmed that the drug release was inversely proportional to membrane weigh but directly related to the initial concentration of pore former in the membrane. Drug release was independent of pH and agitational intensity, but dependent on the osmotic pressure of the release media.[22]

Sadhana RS et al prepared Controlled porosity osmotic pump tablets of Diltiazem hydrochloride by using sodium chloride as osmogen, cellulose acetate and sorbitol as semipremeable membrane and pore former respectively. The effect of concentration of osmogen in core tablet, % pore former, % weight gain, pH of the dissolution medium and agitation intensity on the *in vitro* release was studied.[23]

Indarapu RP formulated Controlled porosity osmotic pump tablets of Baclofen by using the formulation variables such as level of solubility enhancer, ratio of drug to osmogen, coat thickness of semi permeable membrane and level of pore former. The drug release was directly proportional to the level of solubility enhancer, osmotic pressure generated by the osmotic agent and level of pore former and inversely proportional to the coat thickness.[24]

Kazuto O et al studied the purpose of membrane controlling factors responsible for drug release from a controlled-porosity osmotic pump tablet (OPT) that utilizes a sulfobutyl ether-β-cyclodextrin, (SBE)-β-CD, as both a solubilizing and osmotic agent. Chlorpromazine (CLP) was used as a model drug. The present results confirmed that the membrane controlling factors responsible for the drug release were the amount and size of micronized lactose and the amount of triethylcitrate in the membrane.[25]

Kazuto O et al developed a controlled porosity osmotic pump system for poorly water soluble drugs using sulfobutyl ether-b-cyclodextrin sodium salt, (SBE)- β -CD, which can act as both a solubilizing and an osmotic agent. It appears that testosterone release from the device

the presence of (SBE)- β –Cd was mainly due to osmotic pumping while for hydroxypropyl-b-cyclodextrin (HP-β-CD) the major contribution appears to be due to diffusion.[26]

Gregory AM et al investigated a generalized method for conversion of controlled porosity osmotic pump release profiles from first order to zero order kinetics using diltiazem. HCl as a model drug. This high solubility was markedly reduced (155 mg/ml; 37 °C) in the presence of NaCl (1M). This resulted release if 75% of the initial Diltiazem HCl load with zero order kinetics over a 14 to 16 h period.[27]

CONCLUSION

It has been concluded that the oral controlled porosity osmotic pump system contains core tablet coated with semipermeable membrane containing pore forming agents, which can be used to control the drug delivery of poorly water soluble drugs. The drug release form the formulation depends on the type of drug, solubility enhancer used, membrane thickness, concentration of pore forming agent and osmotic agent. The concentration of the pore former, solubility enhancer and osmotic agent are directly proportional and coating membrane thickness is inversely proportional to drug release. The drug release is zero order and independent on physiological properties of the body. So this formulation will be an effective in controlled delivery of drugs.

REFERENCES

1. Chien YW, Novel drug delivery systems. 2nd ed. New York: Marcel Dekker; 2005. 50. 139-296.

2. Banker GS, Rhodes CT. Modern pharmaceutics. 4th ed. New York: Marcel Dekker; 2007, 501-13, 727-52.

3. Manish SW. Controlled released system-A review. 10th Dec 2013, www.pharmainfo.net/reviews/controlled-released-system-review.

4. Sharma S. Osmotic controlled drug delivery system. 20th Dec 2013

Impact Factor = 1.0285

www.pharmainfo.net/reviews/osmotic-controlled-drug-delivery-system.

5. Gohel MC, Parikh RK, Shah NY. Osmotic drug delivery: An update. 10th Dec 2013 www.pharmainfo.net/reviews/osmotic-drug-delivery- update.

6. Vincent M, Joerg O, Nicoletta L, Robert G. "Oral osmotically driven systems: 30 years of development and clinical use", Eur J Pharm Biopharm 2009, 73, 311-323.

7. Forrest Y, Carla MB, Analaysis of variance. The L.L. Thurstone psychometric laboratory University of North Carolina, 2000, 1-8.

8. Makhija SN, Vavia PR, "Controlled porosity osmotic pump-based controlled release systems of pseudoephedrine I. Cellulose acetate as a semi permeable membrane", J Control Release, 2003, 89, 5-18.

9. Chauhan CS, Ranawat MS, Choudhury PK, "Fabrication and evaluation of asymmetric membrane osmotic pump", Indian J Pharm Sci, 2007, 69(6), 748-752.

10. Yueqi BI, Shengjun MAO, Liangchun GAN, Yuanbo LI, Changguang WANG, Nannan XU et al. "A controlled porosity osmotic pump system with biphasic release of theophylline", Chem Pharm Bull 2007, 55(11), 1574-1580.

11. Kanagale P, Lohray BB, Misra A, Davadra P, Kini R, "Formulation and optimization of porous osmotic pump–based controlled release system of oxybutynin", AAPS Pharm Sci Tech, 2007, 8(3), E1-7.

12. Kazuto O, Yuji T, Rinta I, Tetsumi I, Kaneto U, Roger AR et al. "Applicability of (SBE)7m-CD in controlled-porosity osmotic pump tablets", Int J Pharm, 2004, 286, 81-88.

13. Chauhan CS, Choudhury PK, "Controlled porosity osmotic pump for the delivery of Flurbiprofen", Current Drug Delivery 2006, 3, 193-198.

14. Wen-Jen L, Hong-Guann L, "Design of a microporous controlled delivery system for theophylline tablets", J Control Release, 2003, 89, 179-187.

15. Nurten O, Jfilide S, "Design of a controlled release osmotic pump system of ibuprofen", Int J Pharm, 1997, 158, 91-97.

16. Prakash RB, Geetha M, Purushothama N, Utpal S, "Optimization and development of swellable controlled porosity osmotic pump tablet for theophylline", Trop J Pharm Research, 2009, 8(3), 247-255.

17. Zulfequar AK, Rahul T, Brahmeshwar M, "Design and evaluation of enteric coated microporous Osmotic pump tablet (ecmopt) of quetiapine fumarate for the treatment of psychosis", Acta Pol Pharm Drug Res 2012, 69(6), 1125-1136.

18. Rajagopal K, Nallaperumal N, Venkatesan Suba, "Development and evaluation of controlled porosity osmotic pump for Nifedipine and Metoprolol combination", Lipids in Health & Dis, 201, 10(51), 1-13.

19. Ahmed AE, Mina IT, Ahmed Adel AE, "Development and In Vitro/In Vivo Evaluation of Etodolac Controlled Porosity Osmotic Pump Tablets", AAPS pharm scitech, 2011, 12(2), 485-495.

20. Krunal M.U, Atul HK, Ketan VS, "Formulation and evaluation of oral controlled porosity Osmotic pump tablet of methylphenidate HCl", Pharma science monitor Int J Pharm Sci, 2013, 4(3), 20-30.

21. Sanjay M, Nitu C, Krupa M, Rajesh K, Mukesh CG, Ramkishan A, "Formulation, Development and Optimization of Controlled Porosity Osmotic pump tablets of Milnacipran Hydrochloride", IJPRBS 2012, 1(16), 239-259.

22. Fatima SD, Mahesh N, Hasanpasha S, "Formulation and evaluation of controlled porosity osmotic pump for oral delivery of Ketorolac", J Basic Clinical Pharm., 2013, 4(1), 2-9.

23. Sadhana RS, Nityanand SZ, Bhushan G, Shantanu SS, Shivram BS, "Design and development of controlled porosity osmotic

Impact Factor = 1.0285

tablet of Diltiazem hydrochloride", J Adv Pharm Tech & Res., 2012, 3(4), 229-236.

24. Indarapu RP, Veeramalla AK, Rajkumar G, Rajkumar P, Ravikumar G, "Formulation and evaluation of Baclofen controlled porosity osmotic pump tablets", Int. Res. J. Pharm., 2013, 4(5), 181-188.

25. Kazuto O, Atsuo O, Rinta I, Osamu A, Norio O, et al., "Factors affecting membrane controlled drug release for an osmotic pump tablet (OPT) utilizing (SBE)-b-CDas both as solubilizer and osmotic agent', J Control Release, 1999, 60, 311-319.

26. Kazuto O, Roger A.R, Valentino JS, "Release of testosterone from an osmotic pump tablet utilizing (SBE)-b-cyclodextrin as both a solubilizing and an osmotic 7m Pump agent", J Control Release 1999, 58, 29–38.

27. Gregory AM, Steven CS, Karen E, Gaylen MZ, "The solubility modulated osmotic pump: In vitro/in vivo release of diltiazem hydrochloride", Pharmaceutical Research, 1991, 8(1), 88-92.