Research Article [Yellanki *et. al.*, 5(12): Dec., 2014:4091-4095]
CODEN (USA): IJPLCP ISSN: 0976-7126

INTERNATIONAL JOURNAL OF PHARMACY & LIFE SCIENCES
(Int. J. of Pharm. Life Sci.)

# Fabrication and *In Vitro* evaluation of Osmotic pump tablets for Controlled delivery of Diltiazem hydrochloride

**Shiva Kumar Yellanki[1]*, M. Ravi Kumar [1] and Saritha Thatikonda[2]**
1, Department of Pharmaceutics, Geethanjali College of Pharmacy, Cheeryala (V), Keesara (M), Rangareddy, (Telangana) - India
[2] Department of Pharmaceutics, Lalitha College of Pharmacy, Ghatkesar, Venkatapur Village, Rangareddy, (Telangana) - India

## Abstract

The aim of the current study was to design a porous osmotic pump–based drug delivery system for controlled release of Diltiazem Hydrochloride. Based on the principles of an elementary osmotic pump (OP), OP tablets were designed and evaluated with the aim to deliver Diltiazem Hydrochloride in a controlled manner. The tablets were prepared by direct compression method. Effects of coating thickness, surface porosity and viscolyzing polymer were studied. Optimization results indicated that Diltiazem Hydrochloride release was inversely proportional to the membrane thickness and viscolyzing polymer; however directly proportional to the surface porosity of the membrane, respectively. It was concluded that the osmotic pump tablets could provide more prolonged and controlled Diltiazem Hydrochloride release that may result in an improved therapeutic efficacy and patient compliance.

Key-Words: Osmotic pump, Controlled release, Diltiazem Hydrochloride

## Introduction

In recent years, considerable attention has been focused on the development of novel drug delivery systems (NDDS).[1] Once-daily controlled release preparation is often desirable.[2] However, drug release from oral controlled release dosage forms may be affected by pH, gastric motility, and presence of food. One practical approach with a potential to overcome these disadvantages is the osmotic drug delivery system where osmotic materials have been used extensively in the fabrication of drug delivery systems.[3] The historical developments of osmotic systems include seminal contributions such as the Rose-Nelson pump[4], the Higuchi-Leeper pumps[5], the Alzet osmotic pump[6], the elementary osmotic pump (EOP)[7] and the push-pull osmotic pump[8]. The osmotic drug delivery systems suitable for oral administration typically consist of a compressed tablet core that is coated with a semipermeable membrane that has an orifice drilled on it by means of a laser beam.

*** Corresponding Author**
E.Mail: shiva_kmr1984@yahoo.com
Mob.:_91-8500214801

The rate at which the core absorbs water depends on the osmotic pressure generated by the core components and the permeability of the membrane coating. As the core absorbs water, it expands in volume, which pushes the drug solution or suspension out of the tablet through one or more delivery ports.[9] To obviate the need for complicated laser drilling, tablets coated with a membrane of controlled porosity have been described. These membranes consist of a leachable material which dissolves upon contact with water, leaving behind the pores through which the drug solution is pumped out. However, due to the relatively low permeability of the dense coatings, osmotic delivery of drugs with moderate to low solubility is limited.[10]

Diltiazem is a calcium channel blocker widely used for its peripheral and vasodilator properties. It is also used for lowering blood pressure and has some effect on cardiac induction. It is given as oral dosage form in the treatment of angina pectoris and the management of hypertension. Its short biological half life (3-5 h), high aqueous solubility, and frequent administration (usually three to four times a day) make it a potential candidate for sustained release preparations multiple doses are needed to maintain a constant plasma concentration for a good therapeutic response and improved patient compliance. It has also been reported that Diltiazem Hydrochloride absorption in the

duodenum and jejunum is directly proportional to the dose availability.[11, 12]

Hence, the present work was aimed to design, develop and evaluate an oral osmotic delivery system of Diltiazem Hydrochloride, directed towards achieving a better therapeutic effect and bioavailability of this drug.

## Material and Methods

### Materials

Diltiazem Hydrochloride was a gift from Astra Zeneca India Pvt Ltd (Bangalore, India). Potassium chloride (S.D. Fine Chemicals, Mumbai, India), guar gum (H.B.Gum, Kalol, India). Cellulose acetate (CA), Microcrystalline cellulose (MCC), Polyethylene glycol (PEG 400) and sodium lauryl sulphate were also obtained as gifts from Strides Arco Labs Pvt Ltd, Bangalore, India. All other chemicals used in the study were of analytical grade.

### Preparing a controlled-porosity osmotic pump:

### Preparation of core tablets

Core tablets of Diltiazem Hydrochloride were prepared by direct compression method. All the ingredients were weighed accurately, as per Table 1, screened through a sieve of aperture size 250 µm and blended for 5 min using double cone blender (Rimek Kalveka HD-410 AC, Gujarat, India) at 100 rpm to get a uniform mix. Magnesium stearate and talc were added and blended for 2 min. The granules were compressed at a pressure of 5 tons in a laboratory press (Rimek RSB-4, Minipress, Gujarat, India) fitted with size of concave punch set 3-4 mm diameter, respectively.

### Coating of core tablets

Core tablets were film coated with either a semipermeable membrane of 2% (*w/v*) cellulose acetate (CA) in acetone with glycerin (15 %, *m/m*, total solid CA) as plasticizer or with a microporous membrane consisting of PEG 400 (10, 15 and 20, % w*/w*, total solid CA) incorporated in CA using a conventional laboratory model, stainless steel, 10-cm pear shaped, baffled coating pan. The manual coating procedure used was based on an intermittent spraying and drying technique and an orifice through the membrane was made by a microdrill on one side of the tablet.[13]

**Table 1: Composition and Physical parameters of fabricated osmotic pump tablets**

| Ingredient | Formulations | | | | | | |
|---|---|---|---|---|---|---|---|
| | OP1 | OP2 | OP3 | OP4 | OP5 | OP6 | OP7 |
| **Core composition** | | | | | | | |
| Diltiazem Hydrochloride | 25 | 25 | 25 | 25 | 25 | 25 | 25 |
| Guar gum | 0 | 25 | 50 | 50 | 50 | 50 | 50 |
| Potassium Chloride | 25 | 25 | 25 | 25 | 25 | 25 | 25 |
| microcrystalline cellulose | 75 | 75 | 75 | 75 | 75 | 75 | 75 |
| SLS | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
| Talc | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Magnesium stearate | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| **Coating composition** | | | | | | | |
| Cellulose acetate | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| Glycerin | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| PEG 400 | 10 | 10 | 10 | 0 | 15 | 20 | 0 |
| Nature of coating Coat | MP | MP | MP | SP | MP | MP | SP |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Thickness (µm) | 24.5 ±2.1 | 25.5 ±1.6 | 25.7 ±2.7 | 25.7 ±2.7 | 23.7 ±2.5 | 24.7 ±3 | 50.4 ±3.4 |
| Orifice Diameter (µm) | 500 | 500 | 500 | 500 | 500 | 500 | 500 |

*Core composition in mg, Coating composition; %, (*w/v*) CA in acetone, Glycerin (%, *w/w*, total solid CA), PEG 400 (% *w/w*, total solid CA), SLS – sodium lauryl sulphate, SP – semi-permeable, MP – Microporous.

**In Vitro Evaluation**

In vitro studies, in triplicate, were done on USP 24 dissolution apparatus II. The dissolution medium consisted of 900 ml of degassed simulated gastric fluid (SGF, without enzymes) at 37°C ± 0.5°C and 100 rpm stirring. Withdrawn samples were analyzed on a Jasco UV/VIS spectrophotometer (model 7800, Tokyo, Japan) at 275 nm. In vitro studies were conducted to investigate the effect of the following factors on Diltiazem Hydrochloride release from different formulations:

1. Effect of membrane thickness
2. Effect of surface porosity
3. Effect of a viscolyzing polymer

**Statistical analysis**

Experimental results were expressed as mean ±SD values. Student's *t* test was performed to determine the level of significance. Differences were considered to be statistically significant at $p < 0.05$.

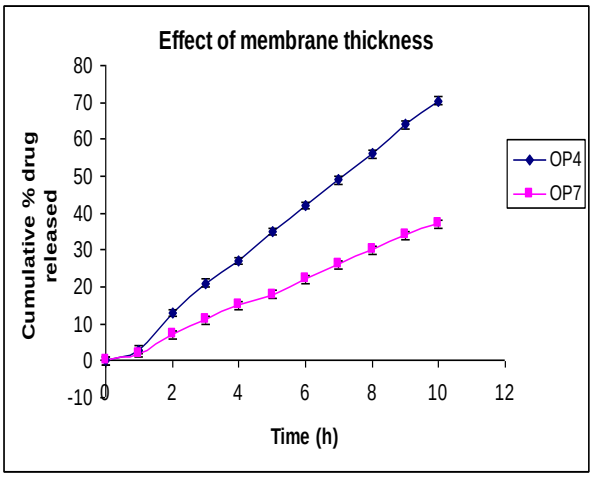
## Results and Discussion

The dosage form developed was designed as a tablet core coated with a rate-controlling membrane. Tablet core consists of drug along with osmogent, polymer and other conventional excipients to form the core compartment. The core compartment is surrounded by a membrane consisting of a semipermeable membrane forming polymer, water-soluble pore-forming additives, and plasticizer capable of improving film-forming properties of the polymers. The semipermeable membrane forming polymer is permeable to aqueous fluids but substantially impermeable to the components of the core. In operation, the core compartment imbibes aqueous fluids from the surrounding environment across the membrane and dissolves the drug.

The assay of drug in various formulations varied between 95.6% and 99.5%. Core tablet weights varied between 150 mg and 160 mg, thickness of the core tablets was found to be in the range of 2.05 and 2.95 mm. The hardness of core tablets was found to be between 4.1 and 5.2 kg $cm^{-2}$, while the friability of prepared core tablets ranged between 0.1% and 0.29%. Thus, all the physical parameters of the compressed matrices were practically within limits.

**Effect of membrane thickness**

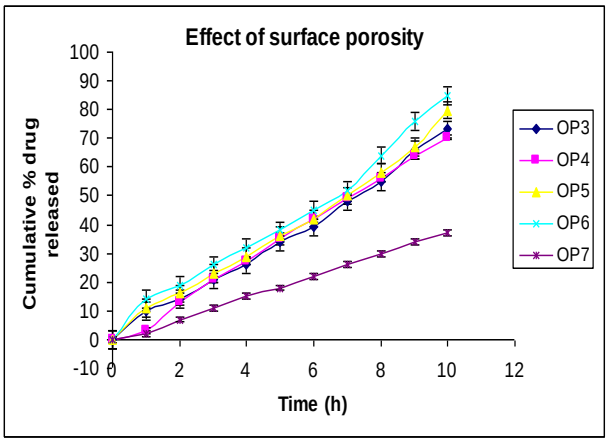
The drug release rate from a microporous membrane was affected by overall membrane thickness. Tablets with varying coating thicknesses were prepared to demonstrate the effect of coating thickness on drug release. The drug release rate changed considerably with a change in coating thickness from 25.5±2.7 to 50.4±3.4 µm. A higher drug release rate was observed for tablets having a 25.5±2.7 coating thickness. An in vitro dissolution profile of tablets with varying coating thicknesses is shown in Fig. 1. From this study, one can conclude that the release rate from an osmotic system is inversely proportional to membrane thickness.




**Effect of surface porosity**

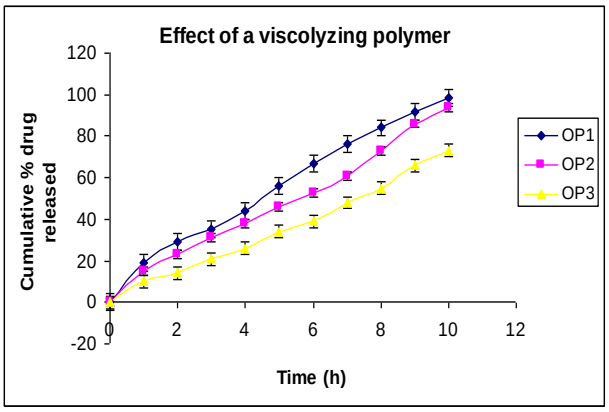
The drug release from the osmotic pump tablets batches OP3, OP5 and OP6 (coated with a membrane that becomes microporous due to dissolution of PEG 400 by the medium), followed the Higuchi kinetics and diffusion mechanism of drug release as compared to OP4 and OP7 batches (coated with a semipermeable membrane) that exhibited zero-order kinetics of drug release. OP3, OP5 and OP6 batches gave higher and non-linear drug release profiles (Fig. 2) due to the fact that when they came in contact with the aqueous environment during the release study, the water soluble PEG 400 leached out leaving behind the microporous membrane on the surface of the core tablet, which allowed free diffusion of drug molecules along the concentration gradient. Membranes in OP4 and OP7

batches behaved like true semi-permeable membranes, resulting in zero-order delivery of drug through the orifice only under the control of osmotic pressure gradient across the membrane.




**Effect of a viscolyzing polymer**

Incorporating viscolyzing polymer that modulate the solubility of the drug within the system can be an ideal approach to control drug release. In this study, guar gum was added to the drug to alter the solubility of Diltiazem Hydrochloride in a dissolution medium and to alter the diffusion of the drug, respectively. A significant change in dissolution was observed with an increase in the viscolyzing agent concentration in the tablets. The drug release rate decreased with an increase in guar gum concentration. In vitro drug release studies revealed that the formulation prepared with 50 mg of a viscolyzing agent (guar gum) fulfills the requirement for prolonging drug release during a period of 10 h (Fig. 3).




## Conclusion

A porous osmotic pump–based drug delivery system can be designed for controlled release of drug Diltiazem Hydrochloride. It is evident from the results that the rate of drug release can be controlled through osmotic pressure of the core, level of pore former, and membrane thickness. Finally, it can be concluded that preparation of osmotic pump tablet can be simplified by coating the core tablet with a pore-forming agent.

## References

1. Shokri J, Ahmadi P, Rashidi P, Shahsavari M, Rajabi-Siahboomi A, Nokhodchi A, Swellable elementary osmotic pump (SEOP): An effective device for delivery of poorly watersoluble drugs, Eur J Pharm Biopharm, 2008, 68, 289-297.
2. Liu L, Che B, Preparation of monolithic osmotic pump system by coating the indented core tablet, Eur J Pharm Biopharm, 2006, 64, 180 - 84.
3. Khan MA, Sastry SV, Vaithiyalingam SR, Agarwal V, Nazzal S, Reddy IK, Captopril gastrointestinal therapeutic system coated with cellulose acetate pseudo latex: evaluation of main effects of several formulation variables, Int J Pharm, 2000, 193, 147-156.
4. Rose S, Nelson JF, A continous long-term injector, Aust J Exp Biol Med Sci, 1955, 33, 415-420.
5. Theeuwes F, Swanson D, Wong P, Bonson P, Place V, Heimlich K, Kwan KC, Elementary osmotic pump for indomethacin, J Pharm Sci, 1982, 72, 253-258.
6. Bittner B, Thelly T, Isel H, Mountfield RJ, The impact of co-solvents and the composition of experimental formulations on the pump rate of the ALZET osmotic pump, Int J Pharm, 2000, 205, 195-198.
7. Higuchi T, Leeper HM, Osmotic dispenser with means for dispensing active agent responsive to osmotic gradient, 1976, US Patent No. 3, 995, 631.
8. Prabakaran D, Singh P, Kanaujia P, Jaganathan KS, Rawat A, Vyas SP, Modified push-pull osmotic system for simultaneous delivery of theophylline and salbutamol: development and in vitro characterization, Int J Pharm, 2004, 284: 95-108.
9. Thombre AG, Appel LE, Chidlaw MB, Daugherity PD, Dumont F, Evans LAF, Sutton SC, Osmotic drug delivery using swellable-core technology, J Cont Rel, 2004, 94, 75-89.
10. Garg A, Gupta M, Bhargava HN, Effect of formulation parameters on the release characteristics of propranolol from asymmetric membrane coated tablets, Eur J Pharm Biopharm, 2007, 67, 725–731.

11. Kendall MJ, Maxwell SR, Sandberg A, Wester gren G, Controlled release metoprolol. Clinical pharmacokinetic and therapeutic implications, Clin Pharmacokinet, 1991, 21, 319-330.
12. Jobin G, Cortot A, Godbillon J, et al, Investigation of drug absorption from the gastrointestinal tract of man, I: metoprolol in stomach, duodenum, and jejunum, Br J Clin Pharmacol, 1985,19,97S-105S.
13. Ramakrishna N, Mishra B, Plasticizer effect and comparative evaluation of cellulose acetate and ethylcellulose-HPMC combination coatings as semipermeable membranes for oral osmotic pumps of naproxen sodium, Drug Dev. Ind. Pharm, 2002, 28, 403–412.

**How to cite this article**
Yellanki S.K., Kumar M.R. and Thatikonda S. (2014). Fabrication and *In Vitro* evaluation of Osmotic pump tablets for Controlled delivery of Diltiazem hydrochloride. *Int. J. Pharm. Life Sci.*, 5(12):4091-4095.
Source of Support: Nil; Conflict of Interest: None declared

**Received: 10.11.14; Revised: 02.11.14; Accepted:09.12.14**