Marmara Pharmaceutical Journal 20: 325-332, 2016
DOI: 10.12991/mpj.20162040694

**ORIGINAL RESEARCH**

# Controlled Porosity Osmotic Tablet of Atenolol: *In-Vitro* and *In-Vivo* Evaluation

Shoaeb Mohammad SYED, Swaroop LAHOTI, Ayaz Ali SYED

**ABSTRACT**

The aim of the present study was to design a controlled porosity osmotic pump tablet of atenolol. The controlled porosity osmotic pump tablet contains pore-forming water-soluble additives in the coating membrane, which after coming in contact with water, dissolve, resulting in an in situ formation of a microporous structure. The dosage regimen of atenolol is 25-mg tablet 2 to 3 times a day. The plasma half-life ranges from ~6 to 7 hours. Hence, Atenolol was chosen as a model drug with an aim to develop a controlled release system for a period of 12 hours. The effect of different formulation variables, namely, ratio of drug to osmogent and level of pore former on the in vitro release was studied by applying a full $3^2$ factorial design. Cellulose acetate (CA) was used as a semipermeable membrane. It was found that drug release was directly related to the amount of osmogent and level of pore former. *In-vivo* study was performed in rabbits and various parameters $C_{max}$, $t_{max}$, AUC, AUMC and MRT were calculated and compared with that of marketed conventional tablet. The optimized formulation was subjected to stability studies as per International Conference on Harmonization (ICH) guidelines and formulation was stable after a 3 month study.

**Keywords:** Atenolol, Controlled Porosity Osmotic pump tablet, Antihypertensive , *In vivo* study

## 1. INTRODUCTION

Conventional preparation is usually administered two or three times a day, which will lead to large fluctuation in drug plasma concentration and side effects on human body. Constant plasma levels can offer a therapeutic advantage for many drugs in terms of both efficacy and tolerance of the treatment [1]. Once-daily controlled release formulations are often desirable. The osmotic pump tablet that holds a prominent place among controlled release systems has many advantages, such as reducing risk of adverse reactions, improving compliance of patients and exhibiting comparable *in vitro/in vivo* drug release. Pharmaceutical agents can be delivered in a controlled pattern over a long period by osmotic pressure; there has been increasing interest in the development of osmotic devices over the past two decades. 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 [2]. The elementary osmotic pump (EOP) consists of an osmotic core, with the drug surrounded by a semipermeable membrane with a delivery orifice. In operation, the osmotic core acts by imbibing water from the surrounding medium via the

Shoaeb Mohammad Syed, Swaroop Lahoti, Ayaz Ali Syed
*Department of Pharmaceutics Y.B. Chavan College of Pharmacy, Dr. Rafiq Zakaria Campus Rauza bagh Aurangabad-431001, India*

**Corresponding author**
Shoaeb Mohammad Syed
*E-mail: ybccpsh@gmail.com*
*Phone: +91 9175599468*

**Submitted / Gönderilme:** 31.03.2016 **Revised / Düzeltme:** 12.07.2016
**Accepted / Kabul:** 14.07.2016

semipermeable membrane. Subsequently, drug solution is generated within the device and delivered out of the device via the orifice [3]. Various attempts to increase the permeability of the semipermeable coating have been reported, such as incorporating water soluble pore-forming additives in the coating. The release rate from these types of systems is dependent on the coating thickness, level of leachable components in the coating, solubility of the drug in the tablet core, and osmotic pressure difference across the membrane but is independent of the pH and agitation of the release media. It was observed that predominantly the drug was released through the pores at a constant rate. It was also observed that most of the core content released through pores at a constant rate, where the mechanism was primarily governed by osmosis with simple diffusion playing a minor role [4-6].

Atenolol, also known as 4-[2-hydroxy-3-[(1-methylethyl) amino]propoxy]benzeneacetamide is a β-blocking agent, could effectively reduce systolic and diastolic blood pressures, and it is widely used alone or in combination to treat hypertension in a dose of 25-mg twice a day. Atenolol is commercially available as conventional tablet. The tablet is usually administered 25 mg two or three times a day, which would lead to large fluctuation in drug plasma concentration and side effect on human body. Controlled release systems are desirable to solve these problems. Among these, osmotic pump tablet offers several advantages, such as reducing risk of adverse reactions, improving compliance of patients and exhibiting comparable *in vitro/ in vivo* drug release The objective of the present study was to develop controlled porosity osmotic pump (CPOP) tablets of atenolol. Lactose:Fructose mixture was used as the osmogent. The tablets were coated with cellulose acetate as the semipermeable membrane containing sorbitol as a pore forming or channeling agent. The formulations were optimized by applying a full $3^2$ factorial design and evaluated for *in-vitro* and *in-vivo* performance.

## 2. MATERIALS AND METHODS

### 2.1. Materials

Atenolol was obtained as a gift sample (Wockhardt Limited, Aurangabad), Fructose and Lactose as osmotic agent (Research fine lab, Mumbai) and microcrystalline cellulose as diluent. Cellulose acetate was employed as a semipermeable membrane (Shreya Life Sciences, Aurangabad), PEG 400 was used as a plasticizer (Thermofisher Scientific Ind Pvt. Ltd, Mumbai), Sorbitol as a pore former (Research fine lab, Mumbai). The atenolol conventional tablet of 50 mg strength (Zydus Cadila Ahmadabad) was used as the reference for comparison. Other chemicals used were of analytical grade.

### 2.2. Analytical method for estimation of Atenolol

Analysis of atenolol was done by UV–Spectrophotometric method at λmax 226.6 nm.

### 2.3. Preparation of core tablet

Tablets were prepared by wet granulation method; the granules were prepared by non-aqueous granulation technique compression was performed 8 mm punch using karnavti multi station tablet compression machine as per the composition in table-3.

### 2.4. Coating of core tablets

The core tablets were coated by using the coating composition as per the formula given in the Table-1, using automated Pharma R & D coater (Instacoat) with rotation speed of 16 to 18 rpm. The spray rate and atomizing air pressure were 2 to 4mL/min and 1 kg/cm$^2$, respectively. Inlet and outlet air temperatures were 50$^0$C and 40$^0$C, respectively. Coated tablets were dried at 50$^0$C and weight gain was kept constant i.e. 3% w/w.

**Table 1.** Coating composition

| Ingredients | Quantity |
|---|---|
| Cellulose acetate | 4 % w/v |
| PEG 400 | 12.5 % w/w |
| Sorbitol | 22 % w/w |
| Acetone :IPA | 90:10 |

### 2.5. Drug content uniformity: (IP 2007)

Ten tablets were weighed and average weight was calculated. All tablets were crushed and powder equivalent to 0.1 g drug and dissolved in 250 ml volumetric flask using 150 ml of methanol the resulting suspension was heated to 60$^0$C and shaken for 15 min cool, and dilute to 250 ml with methanol. Filter through a sintered glass funnel and dilute a suitable volume of filterate with sufficient methanol to produce a solution containing 0.01 % w/v of atenolol. Absorbance of solution was measured at the maximum at 275 nm.

### 2.6. Experimental design

Based on the primary batches factorial design was applied by varying the concentrtation of osmotic agent and pore former and its effects on drug release was studied. Osmotic agent was selected as one of the factor and pore former as other.

D-Optimal design was applied using the software Design-Expert software (Version: 8.0.7.1). Two Factors (Independent variables) were the concentration of osmotic agent (Latose:Fructose) and pore former(Sorbitol). $3^2$ factorial design was applied and 9 different formulations were prepared and evaluated (Table- 2 and 3).

**Table 2.** Factorial Design

| Level | -1 | 0 | +1 |
|---|---|---|---|
| Pore former (Sorbitol) | 18 % | 22 % | 26 % |
| Osmotic agent (Latose:Fructose) | 40 % | 50 % | 60 % |

**Table 3.** Formula for CPOP Tablet of Atenolol

| Ingredients (mg) | F 1 | F 2 | F 3 | F 4 | F 5 | F 6 | F 7 | F 8 | F 9 |
|---|---|---|---|---|---|---|---|---|---|
| Atenolol | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 |
| Lactose | 50 | 62.5 | 75 | 50 | 62.5 | 75 | 50 | 62.5 | 75 |
| Fructose | 50 | 62.5 | 75 | 50 | 62.5 | 75 | 50 | 62.5 | 75 |
| Microcrystalline cellulose | 80 | 55 | 30 | 80 | 55 | 30 | 80 | 55 | 30 |
| PVP K-30 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 |
| IPA | q.s | q.s | q.s | q.s | q.s | q.s | q.s | q.s | q.s |
| Mag.Stearate | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 |
| Talc | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 |
| Coating wt. gain (%) | 3 % | 3 % | 3 % | 3 % | 3 % | 3 % | 3 % | 3 % | 3 % |
| Sorbitol (pore former) | 18 % | 18 % | 18 % | 22 % | 22 % | 22 % | 26 % | 26 % | 26 % |

Concentration of osmotic agent i. e 40 % is with respect to weight of tablet i. e 250 mg

### 2.7. Evaluation parameters

The tablets were evaluated for appearance, shape, uniformity of thickness, diameter, hardness: friability weigh and drug content uniformity.

### 2.8. Dissolution Studies

The release rate of atenolol from CPOP (n=3) was determined from all batches. Batches were evaluated by studying the release study for first 2 hr in 900 ml 0.1 N HCl as dissolution medium, then remaining 10 hrs in 900 ml dissolution medium of phosphate buffer pH 6.8 using USP type II (Paddle) dissolution apparatus (Electrolab TDT) with 50 rpm at 37°C ± 0.5°C. The samples (5 ml) were withdrawn every hour for 12 hrs. The withdrawn samples were replaced with

fresh dissolution medium. The samples were filtered through whatman filter paper and analyzed spectrophotometrically (Shimadzu UV-1800, Japan) at 226.6 nm.

**2.9. Scanning Electron Microscopy (SEM):**

Coating membrane of formulation obtained before and after complete *in-vitro* dissolution of core contents were examined for their porous morphology by scanning electron microscope (SEM). Before dissolution, the tablets were cut with a sharp blade and coating membrane was taken out. This membrane was cleaned with dried cloth to remove any adherent particles and was used for SEM. Similarly, coating membrane was taken out from the tablets after 12 hr of dissolution study and was used for SEM. The coating membrane was carefully washed 3-4 times with water to remove any adherent solid particles. Coating membranes were dried at 45°C for 12 hours and stored between sheets of wax paper in a dessicator until examination.

The small pieces of coating membranes were placed on a spherical brass stub (12 mm diameter) with a double backed adhesive tape in such a way that the outer portion of coating membrane comes in front of electronic beam and was examined under scanning electron microscope.

**2.10. Accelarated Stability Studies**

On the basis of *In vitro* evaluation of all the primary batches for the various parameters, the batch F 5 formulations were packed in strips of 0.04 mm thick aluminum foil laminated with polyvinyl chloride (PVC) and stored in ICH certified stability chambers for the accelerated stability studies. The stability of the tablets was studied for the duration of 90 days at temperature $40^0C \pm 2^0C$ and 75% ± 5% relative humidity.

**2.11. In-vivo Study: (Pharmacokinetic study)**

Protocol for animal study was approved by Institutional Animal Ethical Committee of YB Chavan College of Pharmacy Aurangabad with approval no. (CPCSEA/IAEC/P'ceutics-15/2011-12/52).

*In-vivo* study was performed to estimate various pharmacokinetic parameters and comparison was made between conventional conventional marketed tablet and formulated CPOP tablet of atenolol in rabbit plasma using UV Spectroscopic method**.**

**2.12. Animals**

The study was carried out using adult male Albino rabbits (weight 1.5-2 kg) in two groups of three animals each (n=3). The animals were housed under standard condition with a 12 hr light/dark cycle with free access of water before study.

**2.13. Recovery study**

Atenolol stock solution (100µg/ml) was prepared in pH 6.8 phosphate buffer .Then working solutions were prepared by diluting the stock solution in pH 6.8 phosphate buffer.100 µl of these serial dilutions were transferred into 1.5 ml Eppendrof tubes and the solvent were evaporated to dryness. The resulted samples were then used to spike blank rabbit plasma (100 µl) and the procedure done as described in 7.5. Calibration curve at 2.5, 5 and 10 µg/ml atenolol in rat plasma was generated having regression coefficient 0.998.

**2.14. Administration of tablets and collection of plasma**

The rabbits were fasted with water access for 12 hr prior to initiation of study. Group–I was administered with 50 mg conventional marketed tablet of atenolol (ATEN-50) using applicator along with 5 ml of water. Group-II was administered with formulated CPOP 50 mg tablet of atenolol (F 5 formulation) in the similar manner. The blood samples were withdrawn from marginal ear vein of rabbit through a syringe with 24 gauge needle just before and at 1, 2, 4, 6, 8, 10 and 12 hr after dosing. Each time 1 ml of blood was withdrawn.

**2.15. Sample extraction and analytical procedure**

After collection the samples were subjected to centrifugation in micro centrifuge at 4000 rpm for 8 min to separate plasma, form this separated plasma 500 µl was taken and alkalify with 100 µl of 0.1N NaOH and vortex vigorously for 3 min using vortex mixture. Ethyl acetate (1 ml) was then added to the mixture and vortex again for 5 min to extract atenolol. The samples were centrifuged at 4000 rpm for 8 min to separate the organic layer. The organic layer was collected and evaporated to dryness at room temperature. The residue was reconstituted in 5 ml of pH 6.8 phosphate buffer, vortex-mixed for 1 min and analyzed at 226.6 nm using UV Spectrophotometer. Plasma atenolol concentrations were determined by ultraviolet spectroscopy (UV-1800 SHIMADZU UV SPECROPHOTOMETER). The detection wavelength was 226.6 nm and the solvent was pH 6.8 phosphate buffer.

**2.16. Estimation of Parameters**

The parameters like $C_{max}$, $t_{max}$, AUC, AUMC and mean residence time (MRT) were calculated by using MathCAD.

## 3. RESULTS AND DISCUSSION

The core tablet formulations were evaluated for various parameters and the results revealed as per table– 4.

**Table 4.** Results of evaluation parameters

| Batch Code | Thickness, Diameter | Friability (%) | Hardness (Kg/ cm²) | Uniformity of weight (mg) | Drug content (%) |
|---|---|---|---|---|---|
| F 1 | 4.48± 0.01 mm thickness, 8.5 mm diameter | 0.43 ± 0.03 | 4.2 ± 0.57 | 245 ± 2.09 | 99.01±1.10 |
| F 2 | 4.51 ± 0.04 mm thickness, 8.5 mm diameter, | 0.55 ± 0.02 | 5.1 ± 0.76 | 248 ± 1.48 | 101.25±1.12 |
| F 3 | 4.48 ± 0.03 mm thickness, 8.5 mm diameter | 0.27 ± 0.01 | 4.6 ± 0.88 | 253 ± 2.47 | 101.91±0.64 |
| F 4 | 4.47 ± 0.05 mm thickness, 8.5 mm diameter, | 0.74 ± 0.04 | 4.9 ± 0.54 | 251 ± 1.98 | 103.23±1.08 |
| F 5 | 4.47 ± 0.08 mm thickness, 8.5 mm diameter | 0.65 ± 0.02 | 4.8 ± 0.58 | 247 ± 2.86 | 99.45±0.19 |
| F 6 | 4.51 ± 0.04 mm thickness, 8.5 mm diameter, | 0.43 ± 0.03 | 5.1 ± 0.76 | 248 ± 1.48 | 99.39±1.10 |
| F 7 | 4.48 ± 0.03 mm thickness, 8.5 mm diameter | 0.27 ± 0.01 | 4.9 ± 0.54 | 251 ± 1.98 | 99.69±0.52 |
| F 8 | 4.48± 0.01 mm thickness, 8.5 mm diameter | 0.43 ± 0.03 | 4.6 ± 0.88 | 253 ± 2.47 | 101.91±0.64 |
| F 9 | 4.50 ± 0.02 mm thickness, 8.5 mm diameter | 0.13 ± 0.50 | 5.3 ± 0.43 | 258 ± 2.06 | 102.78±1.54 |

*All values are means ± SD, n=3;

**Table 5.** Drug release profiles of F 1 to F 9

| Time (Hr) | F 1 | F 2 | F 3 | F 4 | F 5 | F 6 | F 7 | F 8 | F 9 |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 9.877 ± 0.72 | 10.996 ±0.47 | 11.443 ±0.49 | 10.772 ±0.62 | 13.457 ±0.66 | 13.849 ±0.72 | 11.611 ±0.55 | 11.947 ±0.7 0 | 15.863 ±0.85 |
| 2 | 15.806 ±1.11 | 17.715 ±1.02 | 17.158 ±0.89 | 17.546 ±0.70 | 20.190 ±0.80 | 20.248 ±0.85 | 16.375 ±0.72 | 16.377 ±0.50 | 23.337 ±1.5 |
| 3 | 22.216 ±0.56 | 21.282 ±0.70 | 23.799 ±0.99 | 21.000 ±1.10 | 27.351 ±0.66 | 27.969 ±0.48 | 22.508 ±0.60 | 25.979 ±0.68 | 32.306 ±0.52 |
| 4 | 29.780 ±0.72 | 30.127 ±0.90 | 30.196 ±0.84 | 29.788 ±0.92 | 37.685 ±0.45 | 38.698 ±0.90 | 29.850 ±0.8 3 | 32.053 ±0.35 | 39.925 ±0.90 |
| 5 | 37.273 ±0.85 | 37.398 ±0.87 | 37.132 ±0.30 | 37.001 ±0.80 | 40.522 ±0.21 | 41.317 ±0.38 | 37.959 ±0.43 | 37.992 ±0.34 | 42.383 ±0.42 |
| 6 | 42.401 ±0.95 | 42.863 ±0.90 | 43.043 ±0.55 | 42.519 ±0.85 | 46.619 ±0.36 | 47.530 ±0.51 | 43.035 ±0.80 | 49.167 ±0.54 | 53.693 ±0.85 |
| 7 | 50.354 ±0.66 | 50.594 ±0.30 | 50.831 ±0.60 | 50.361 ±0.52 | 50.510 ±0.72 | 51.202 ±0.47 | 50.823 ±0.66 | 53.240 ±0.87 | 61.427 ±1.08 |
| 8 | 62.266 ±1.45 | 62.396 ±1.02 | 62.522 ±0.99 | 62.105 ±0.79 | 61.863 ±0.95 | 62.055 ±1.48 | 62.458 ±0.51 | 62.147 ±0.55 | 66.070 ±0.65 |
| 9 | 66.299 ±0.45 | 66.541 ±0.79 | 66.388 ±0.55 | 66.193 ±0.98 | 64.437 ±0.60 | 69.610 ±1.67 | 66.659 ±0.93 | 64.611 ±0.48 | 69.394 ±0.56 |
| 10 | 69.344 ±0.65 | 69.979 ±1.20 | 70.553 ±0.40 | 69.685 ±0.45 | 69.542 ±0.21 | 74.631 ±1.73 | 69.931 ±0.50 | 69.661 ±0.62 | 79.617 ±1.10 |
| 11 | 73.412 ±0.79 | 74.274 ±0.94 | 75.410 ±0.70 | 74.146 ±0.85 | 78.254 ±0.89 | 83.371 ±1.50 | 74.281 ±0.95 | 78.374 ±1..20 | 89.950 ±0.65 |
| 12 | 77.388 ±0.52 | 78.926 ±1.28 | 82.027 ±0.30 | 78.350 ±0.73 | 87.851 ±0.33 | 90.367 ±1.48 | 78.598 ±1.04 | 88.084 ±0.52 | 95.694 ±1.14 |

*All values are means ± SD, n=3;

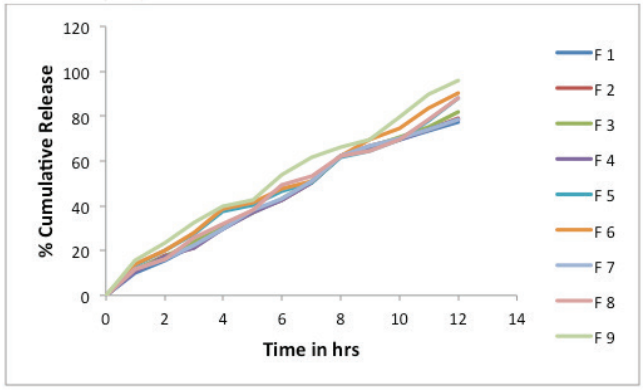


**Figure 1.** Comparison of *in vitro* release of batches F 1 to F 9

Formulation F1 shows less release as compared to other batches because F1 contains fewer amounts of pore former and osmogent while F9 contains high concentration of pore former and osmogent hence it shows highest release amongst all other formulations.

### Surface Response Plot

**Table 6.** ANOVA for response surface 2FI model

| Source | Sum of squares | df | Mean square | F-value | P value prob>F | |
|---|---|---|---|---|---|---|
| Model | 324.94 | 3 | 108.31 | 29.86 | 0.0013 | Significant |
| A-osmotic agent | 189.87 | 1 | 189.87 | 52.35 | 0.0008 | Significant |
| B-sorbitol | 96.28 | 1 | 96.28 | 26.55 | 0.0036 | Significant |
| AB | 38.79 | 1 | 38.79 | 10.70 | 0.0222 | Significant |
| Residual | 18.13 | 5 | 3.63 | | | |
| Core total | 343.07 | 8 | | | | |

**Equation:**

**% Drug release(Y) = +84.14+5.63×A+4.01×B+3.11×A×B**

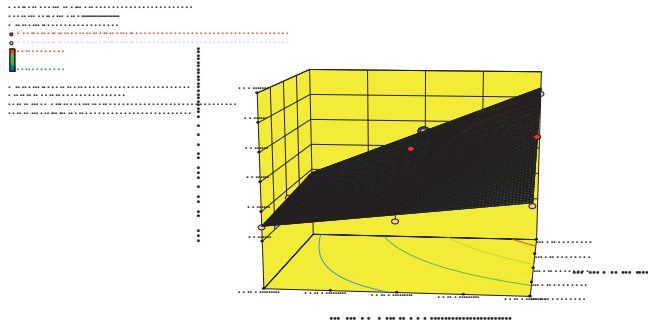

**Figure 2.** Surface Response Curve

Surface response plot shows a positive coefficient to both the factors.

### Effect of Concentration of Osmogent

From the release profile, it is clear that increase in the concentration of osmotic agent, greater the driving force and enhances the release of drug and thus had a direct effect on drug release.

### Effect of Pore Forming Level

It is clearly evident that the level of sorbitol had a direct effect on drug release. As the level of pore former increases, the membrane becomes more porous after coming into contact with the aqueous environment, resulting in faster drug release.

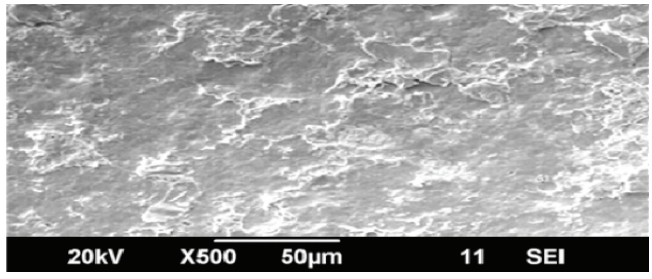


**Figure 3.** SEM micrograph of coating membranes of F 5 formulation Before dissolution

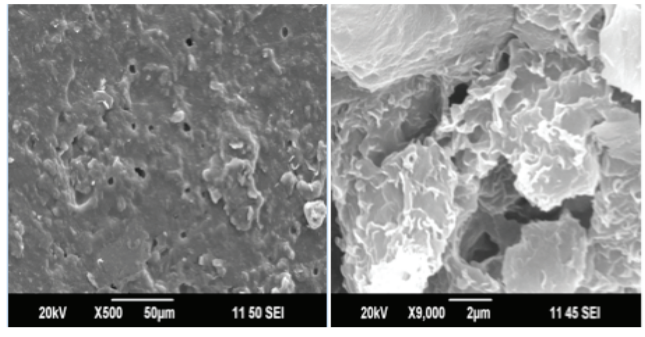


**Figure 4.** SEM micrograph of coating membranes of F 5 formulation After dissolution.

Fig. 3 indicates SEM image of coating membrane before dissolution it shows that there is no any evidence of pores formation where as Fig. 4 clearly indicates after coming in contact with dissolution medium pores were formed and predict the mechanism of controlled porosity osmotic tablet by pore formation.

### *In-Vivo* Study (Pharmacokinetic Study)

**Table 7.** Measurement of atenolol in spiked rabbit plasma

| Nominal concentration (µg/ml) | % Recovery |
|---|---|
| 2.5 | 93.75±1.10 |
| 5 | 93.00±0.65 |
| 10 | 95.31±0.52 |

*All values are means ± SD, n=3;

**Table 8.** Concentration of atenolol in plasma (µg/ml)

| Time (Hr) | Conventional (Aten-50) | CPOP Tablet |
|---|---|---|
| 1 | 64.12±0.75 | 26.71±0.20 |
| 2 | 110.93±0.19 | 43.97±0.78 |
| 4 | 80.31±0.25 | 79.37±0.32 |
| 6 | 51.96±0.48 | 95.62±0.65 |
| 8 | 31.32±0.55 | 90.46±0.50 |
| 10 | 20.24±0.60 | 52.12±0.52 |
| 12 | 11.09±0.10 | 32.34±0.18 |

*All values are means ± SD, n=3;

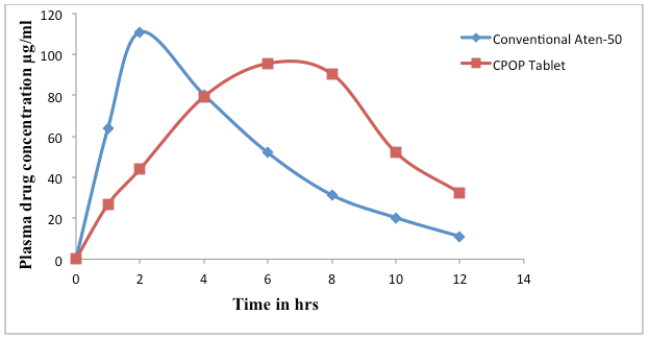


**Figure 5.** Plasma concentration time profile curve of atenolol for marketed conventional and CPOP Tablet

**Table 9.** Pharmacokinetic parameters of atenolol for marketed and CPOP Tablet

| Parameters | IR Aten-50 | CPOP Tablet |
|---|---|---|
| $C_{max}$(µg/ml) | 110.93 | 95.62 |
| $t_{max}$(hrs) | 2 | 6 |
| $AUC_{0-12h}$(h µg/ml) | 609.41 | 766.331 |
| $AUMC_{0-12h}$(h µg/ml) | 2725 | 4833 |
| MRT(hrs) | 4.47 | 6.90 |

### Accelarated Stability Studies

The stability of the tablet formulation (F 5) was studied for the duration of 90 days at temperature $40^0C±2^0C$ and 75%±5% relative humidity. The tablets was then evaluated for various parameters viz. thickness, hardness, and drug content and release studies. Following results were oberved.

**Table 10.** Stability evaluation

| Batch Code | Thickness, Diameter | Hardness (Kg/ $cm^2$) | Uniformity of weight (mg) | Drug content |
|---|---|---|---|---|
| F 5 | 4.47 ± 0.08 mm thickness, 8.5 mm diameter | 4.8 ± 0.58 | 247 ± 2.86 | 99.45±0.19 |

*All values are means ± SD, n=3

**Table 11.** Drug release profiles of F 5

| Time (Hr) | % Dissolution For 0 Days | (n ± SD)* For 90 Days |
|---|---|---|
| 1 | 13.457 ±0.66 | 12.157 ±0.95 |
| 2 | 20.190 ±0.79 | 19.281 ±0.32 |
| 3 | 27.351 ±0.56 | 26.131 ±0.40 |
| 4 | 37.685 ±0.45 | 36.295 ±0.56 |
| 5 | 40.522 ±0.21 | 40.012 ±0.85 |
| 6 | 46.619 ±0.36 | 45.329 ±0.55 |
| 7 | 50.510 ±0.55 | 49.213 ±0.42 |
| 8 | 61.863 ±0.72 | 61.00 ±0.58 |
| 9 | 64.437 ±0.95 | 63.577 ±0.99 |
| 10 | 69.542 ±0.60 | 69.121 ±1.06 |
| 11 | 78.254 ±0.35 | 77.334 ±0.48 |
| 12 | 87.851 ±0.33 | 86.293 ±0.95 |

*All values are means ± SD, n=3

From Table 10 it can be seen that there is no change in the evaluation parameter of the tablet during the 3 month. Table 11 showed, that a slight decrease release of drug, but it is negligible. Hence, stability studied revealed that formulation F 5 may stable for 3 month.

**Acknowledgement**

We are thankful to Wockhardt limited Waluj, Aurangabad for providing gift sample of atenolol. We are also thankful to Padmashree Mrs. Fatema Rafiq Zakaria for providing facility to carry out this work.

**Ethical Approvals**

Institutional Animal Ethical Committee of Y B Chavan College of Pharmacy Aurangabad with approval no. (CPCSEA/IAEC/P'ceutics-15/2011-12/52).

**Atenolol'un Kontrollü Gözenekli Ozmotik Pompa Tabletleri: *in-vitro* ve *in-vivo* uygulamalar**

**ÖZ**

Bu çalışmanın amacı atenolol'un Kontrollü Gözenekli Ozmotik Pompa tabletlerinin tasarlanmasıdır. Kontrollü Gözenekli Ozmotik Pompa tabletleri kaplama membranında suyla temas ettikten sonra suda çözünebilen gözenek oluşturucular içermektedir ve çözünme sonucunda mikroporlu yapı *in situ* olarak oluşur. Atenolol'un doz rejimi 6 – 7 saattir. Bu nedenle atenolol, 12 saat boyunca ilaç serbestleştirebilen bir kontrollü salım sistemi oluşturmak için model ilaç olarak seçilmiştir. *In vitro* ilaç serbestleşmesi üzerine farklı formülasyon değişkenlerinin etkisi yani ilaç-ozmojen oranı ve gözenek oluşturucu seviyesi $3^2$ faktoriyal tasrım uygulanarak çalışılmıştır. Yarı geçirgen membran olarak selüloz asetat (CA) kullanılmıştır. Sonuçta ilaç serbestleşmesi üzerine ozmojen miktarının ve gözenek oluşturucu seviyesinin doğrudan etkili olduğu bulunmuştur. *In vivo* çalışmalar tavşanlarda yapılmış, $C_{max}$, $t_{max}$, AUC, AUMC ve MRT hesaplanmış ve konvansiyonel piyasa tabletiyle karşılaştırılmıştır. Optimize formülasyon Uluslararası Harmonizasyon Komitesi'nin (ICH) klavuzlarına bağlı kalınarak stabilite çalışmalarına maruz bırakılmış ve formülasyonun 3 ay sonunda stabil kalmıştır.

**Anahtar kelimeler:** Atenolol, Kontrollü Gözenekli Ozmotik Pompa Tabletler, Antihipertansif, *In vivo* uygulamalar

**References**

1. Theeuwes F. Elementary osmotic pump. J Pharm Sci 1975; 64: 1987-91.
2. Zentner GM, McClelland GA, Sutton SC. Controlled porosity solubility and resin-modulated osmotic drug delivery systems for release of diltiazem hydrochloride. J Control Release1991; 16:237-44.
3. Santus G, Baker WR. Osmotic drug delivery: a review of patent literature. J Control Release 1995; 35:1-21.
4. Herbig SM, Cardinal JR, Korsmeyer RW, Smith KL. Asymmetric-membrane tablet coatings for osmotic drug delivery. J Control Release 1995;35:127-36.
5. Zentner GM, Rork GS, Himmelstein KJ. Controlled porosity osmotic pump. US patent 4 968 507. November 6, 1990.
6. Ajay B, Prasada, R., Vijaya, RJ. Controlled-Porosity Osmotic Pump Tablets-An Overview. Interrnational J Pharm Pharm Sci 2010; 2: 114-26.
7. Chai, HF, Xu J, Liu GC. Sodium salicylate micro-porous osmotic pump controlled release tablet. J Guangdong College Pharm 2008;3:22-5.
8. Edavalath S, Shivanand K., Kalyani PM, Prakash R, Goli D.Formulation Development and Optimization of Controlled Porosity Pump Tablet of Diclofenac Sodium. Int J Pharm Pharm Sci 2011;3:80-7.
9. Hui L, Xing-Gang Y, Shu-Fang N, Lan-Lan W, Wei-San P. Chitosan based controlled porosity osmotic pump for colon-specific delivery system: Screening of formulation variables and in vitro investigation. Int J Pharm 2007; 332:115–24.
10. Jianping L, Junting J, Chendong D, Wenli Z, Yanxia C. Evaluation of pharmacokinetic and pharmacodynamic relationship for oral sustained-release atenolol pellets in rats. J Pharm Biomed Anal 2011; 55: 342–8.
11. Mahalaxmi R, Phanidhar S, Ravikumar A, Pritam K, Narkhede A. Enhancement of Dissolution of Glipizide from Controlled Porosity Osmotic Pump Usinga Wicking Agent and a Solubilizing Agent. Int J Pharm Tech Res 2009;1: 705-11.
12. Makhija SN, Vavia PR.Controlled porosity osmotic pump-based controlled release systems of Pseudoephedrine I. Cellulose acetate as a semipermeable membrane. J Control Release 2003; 89:5–18.
13. Meena R, Rahul S, Chelladurai S, Brhameshwar M. Development and biopharmaceutical evaluation of osmotic pump tablets for controlled delivery of diclofenac sodium. Acta Pharm 2003; 53:263–73.
14. Pandey S, Viral D. Formulation and Evaluation of Osmotic Pumps An Overview. Pharm Lett 2010; 2:189-95.
15. Pramod K, Sanjay S, Brahmeshwar M. Development and Evaluation of Elementary Osmotic Pump of Highly Water Soluble Drug: Tramadol Hydrochloride. Curr Drug Deliv 2009; 6:130-4.
16. Pritam K, Braj BL, Ambikanandan M, Prakash D, Rajesh K. Formulation and Optimization of Porous Osmotic Pump–based Controlled Release System of Oxybutynin. AAPS PharmSciTech 2007; 8:44-8.
17. Punitha S, Garaga S. Formulation and evaluation of Porous Osmotic Pump based Release System of Oxybutynin. Int J Pharm Tech Res 2010; 2:1723-32.
18. Verma RK, Kaushal AM, Garg S. Development and evaluation of extended release formulations of isosorbide mononitrate based on osmotic technology. Int J Pharm 2003; 263: 9–24.