



Research Article

**DEVELOPMENT AND *IN-VITRO* DISSOLUTION STUDIES OF BILAYER TABLET OF METOPROLOL SUCCINATE (SR) AND HYDROCHLOROTHIAZIDE (IR)**

Raman Tativaka\*, S. Jaya prakash, Subhakar.M, Anil Kumar.P, Jyothi.D  
Dept of Pharmaceutics, K.M College of Pharmacy, Madurai.

(Received: 7 March, 2012; Accepted: 15 March, 2012; Published: 29 April, 2012)

\*Corresponding author's email: [ramantativaka@gmail.com](mailto:ramantativaka@gmail.com)

**ABSTRACT**

Bilayer tablets of Hydrochlorothiazide (IR) Metoprolol succinate (SR) were formulated for the management of hypertension. In the formulation of immediate release Micro crystalline cellulose and starch were used as super disintegrant and was directly compressed. For sustained release portion HPMC polymers were used in granulation stage and also extragranularly. Preformulation studies were performed prior to compression. The compressed bilayer tablets were evaluated for weight variation, thickness, hardness, friability, drug content, and *in-vitro* drug release using USP dissolution apparatus type 2 (paddle) by using HPLC method. It was found that the optimized formulation F-7 showed 17.34%, 33.06%, 55.35%, 97.78% release for Metoprolol succinate in 1, 4, 8, 20 hours respectively. However, Hydrochlorothiazide was released 95.29% at the end of 60 minutes, and DSC studies have done and show no interaction between the drug and polymer. The stability studies were carried out for the reproducibility batches F-8 and F-9 for 60 days and it showed acceptable results. The Bilayer tablet technology can be successfully applied for sustained release of Metoprolol Succinate and immediate-release of Hydrochlorothiazide.

**Key words:** Hydrochlorothiazide, Metoprolol succinate, Bilayer tablet.

**INTRODUCTION**

In the recent times, multi-layer matrix tablets are gaining importance in the design of oral controlled drug delivery systems. Bi-layer tablets are novel drug delivery systems where combination of two or more drugs in a single unit. They

are preferred for the following reasons to co-administer two different drugs in the same dosage form, to minimize physical and chemical incompatibilities, for staged drug release, IR and SR in the same tablet, for chronic condition requiring repeated dosing. In the present study a combination

drug therapy is recommended for treatment of hypertension to allow medications of different mechanism of action to complement each other and together effectively lower blood pressure at lower than maximum doses of each. The rationale for combination therapy is to encourage the use of lower doses of drug to reduce the patient's blood pressure, minimize dose dependent side effects and adverse reactions.

Metoprolol is selective  $\beta_1$  receptor blocker used in the treatment of hypertension and angina pectoris. It reduces plasma renin activity in hypertensives. It has half life of 3 to 4 hours in fast hydroxylator and about 7 hour in slow hydroxylators. Hence to improve its therapeutic efficacy and patient compliance the formulation of metoprolol succinate as sustained release is necessary for chronic use.

Hydrochlorothiazide is a first line diuretic drug of the thiazide class that acts by inhibiting the kidney's ability to retain water. This reduces the volume of the blood, decreasing lower peripheral vascular resistance.

#### **MATERIALS AND METHODS**

Metoprolol succinate, Hydrochlorothiazide, HPMC K4M, HPMC K 100, Polyvinyl pyrrolidone, Microcrystalline cellulose, Maize Starch, Aerosil, Purified talc, Magnesium stearate were received from Madras Pharmaceuticals, Chennai. Brilliant

Blue lake was received as a gift sample from Roha diechemicals. All other chemicals are of analytical grades.

#### **Formulation**

##### **Manufacturing process of Metoprolol Succinate sustained release granules**

Weighed quantity of Metoprolol Succinate, Microcrystalline cellulose PH102, Hydroxy propyl methyl cellulose K100M and Hydroxy propyl methyl cellulose K4M were sifted through #30 mesh sieve and mixed for 10 minutes in rapid mixer granulator.

The binder solution containing poly vinyl pyrrolidone K30 in Isopropyl alcohol was added slowly to the above ingredients and mixed at slow speed, after complete addition of binder solution mix well to get the granules. The wet granules were loaded in a fluidized bed drier and dried till the moisture content of granules are between 2.0 to 3.0. The dried granules were sifted through #20 mesh sieve, Hydroxy propyl methyl cellulose K100, Hydroxy propyl methyl cellulose K4M, Colloidal silicon dioxide and purified talc were loaded in planetary mixer along with the dried granules and mixed well for 3 minutes at slow speed.

##### **Manufacturing process of Hydrochlorothiazide Immediate Release granules**

Weighed quantity of Hydrochlorothiazide, Microcrystalline cellulose PH102, Lactose DCL 11 and Maize starch were sifted through #30 mesh sieve and mixed for 10 minutes in Hexagonal blender. Colloidal silicon dioxide and magnesium Sterate sift through #30 mesh and Brilliant blue lake sift through #100 mesh were loaded in blender along with the above sifted material and mixed well for 2 minutes at slow speed.

#### **Evaluation of Granules Flow Properties**

1, 2

The prepared granules were evaluated for parameters like bulk density, tap density, Carr index, Angle of repose, and Hausner's ratio. The results are as in table 3 and 4.

#### **Compression of Bilayer tablets:**

The quantity of granules for the immediate-release layer was compressed lightly using 27 stationary double rotary compression machine (Cad mach, India) using 14/32 inch circular shaped plain punches. Over this compressed layer, required quantity of the sustained release layer was placed and compressed to obtain hardness in the range of 8-12 kg/cm<sup>2</sup> to form a bilayer tablet of sustained release of Metoprolol succinate and immediate release of Hydrochlorothiazide. Then the compressed bilayer tablets were evaluated.

#### **Evaluation of Metoprolol succinate and Hydrochlorothiazide:**

Metoprolol and Hydrochlorothiazide granules of bulk density, tapped density, Carr's index, Hausner ratio, angle of repose and moisture content were evaluated. Their results are tabulated in table no.3 and 4.

#### **ASSAY BY HPLC<sup>3</sup>**

Assay for Metoprolol Succinate and Hydrochlorothiazide:

#### **Chromatographic system:**

Apparatus: HPLC, PDA detector, Column: Inertsil ODS C18, 250× 4.6 mm, 5μ, Flow rate: 1.0 ml/min, Wave length: 222 nm, Injection volume: 20μl, Column temperature: Ambient, Diluent: 1<sup>st</sup> diluents –Methanol and 2<sup>nd</sup> diluents – Mobile phase, Mobile phase : Mix 85 parts of Buffer and 15 parts of Acetonitrile

#### **Preparation of standard solution:**

Accurately weighed 23.5mg of Metoprolol succinate and 12.4mg Hydrochlorothiazide was taken in 100ml volumetric flask and to this 50ml of methanol was added and sonicated to dissolve and volume was made up with methanol. From this 5ml of above solution was pipetted out in to 50 ml volumetric flask and volume was made up with mobile phase.

**Table: 1: Formulation of Metoprolol succinate sustained release granules**

| Sl. No                   | Ingredients                                  | F-1    | F-2    | F-3    | F-4    | F-5    | F-6    | F-7    | F-8    | F-9    |
|--------------------------|--|--------|--------|--------|--------|--------|--------|--------|--------|--------|
|                          |  | mg/tab |
| 1                        | Metoprolol succinate                         | 23.75  | 23.75  | 23.75  | 23.75  | 23.75  | 23.75  | 23.75  | 23.75  | 23.75  |
| 2                        | Microcrystalline cellulose pH 101            | 100    | 90     | 87     | 88     | 90     | 87     | 87     | 87     | 87     |
| 3                        | Hydroxy propyl methyl cellulose (HPMC K100M) | 50     | 40     | 43     | 45     | 56     | 44     | 56     | 56     | 56     |
| 4                        | Hydroxypropyl methyl cellulose (HPMC K4M)    | --     | 20     | 21     | 15     | --     | 22     | 12     | 12     | 12     |
| 5                        | Polyvinyl pyrrolidone                        | 10     | 15     | 15     | 17     | 18     | 14     | 15     | 15     | 11     |
| 6                        | Iso propyl Alcohol                           | q.s    |
| <b>Lubrication Stage</b> |  |        |        |        |        |        |        |        |        |        |
| 7                        | Hydroxypropyl methyl cellulose (HPMC K100M)  | 58     | 58     | 43     | 44     | 47     | 42     | 46     | 46     | 46     |
| 8                        | Hydroxypropyl methyl cellulose (HPMC K4M)    | --     | --     | 15     | 15     | 13     | 15     | 6.7    | 6.7    | 6.7    |
| 9                        | Purified talc                                | 2      | 1.75   | 1.25   | 1.25   | 1.25   | 1.25   | 1.25   | 1.55   | 1.55   |
| 10                       | Hydroxy propyl cellulose                     | 1.25   | 1.5    | 1      | 1      | 1      | 1      | 1      | 2      | 2      |

**Table: 2 Formulation of Hydrochlorothiazide Immediate release granules**

| Sl. No | Ingredients                       | F-1 mg/tab | F-2 mg/tab | F-3 mg/tab | F-4 mg/tab | F-5 mg/tab |
|--------|-----------------------------------|------------|------------|------------|------------|------------|
| 1.     | Hydrochlorothiazide               | 12.50      | 12.50      | 12.50      | 12.50      | 12.50      |
| 2.     | Microcrystalline cellulose pH 102 | 66.90      | 70.25      | 70.25      | 73.00      | 73.00      |
| 3.     | Maize starch                      | --         | 5.00       | 5.00       | 5.00       | 15.00      |
| 4      | Colloidal silicon dioxide         | --         | --         | 1.25       | 1.25       | 3.00       |
| 5.     | Lactose DCL 11                    | 44.50      | 40.50      | 35.00      | 35.00      | 20.00      |
| 6.     | Magnesium stearate                | 0.50       | 0.50       | 0.50       | 0.625      | 1.00       |
| 7.     | Brilliant Blue lake               | 0.50       | 0.50       | 0.50       | 0.50       | 0.50       |

**Table: 3 Evaluation of Metoprolol succinate granules:**

| Sl. No | Formulation code | Bulk density g/cc | Tapped density g/cc | Carr's index (%) | Hausner's Ratio | Angle of Repose (degree) | Moisture content (%) |
|--------|------------------|-------------------|---------------------|------------------|-----------------|--------------------------|----------------------|
| 1.     | F-1              | 0.654             | 0.746               | 12.33            | 1.14            | 27.42                    | 2.2                  |
| 2.     | F-2              | 0.664             | 0.758               | 12.40            | 1.14            | 27.69                    | 2.4                  |
| 3.     | F-3              | 0.679             | 0.778               | 12.72            | 1.15            | 27.84                    | 2.3                  |
| 4.     | F-4              | 0.679             | 0.759               | 14.23            | 1.17            | 27.69                    | 2.2                  |
| 5.     | F-5              | 0.648             | 0.758               | 14.51            | 1.17            | 27.15                    | 2.1                  |
| 6.     | F-6              | 0.651             | 0.741               | 12.51            | 1.14            | 26.58                    | 2                    |
| 7.     | F-7              | 0.668             | 0.758               | 11.87            | 1.13            | 25.11                    | 2.4                  |
| 8.     | F-8              | 0.649             | 0.736               | 11.82            | 1.13            | 25.31                    | 2.5                  |
| 9.     | F-9              | 0.668             | 0.758               | 11.87            | 1.13            | 25.31                    | 2.4                  |

**Table: 4 Evaluation of Hydrochlorothiazide granules:**

| Sl. No | Formulation code | Bulk density g/cc | Tapped density g/cc | Carr's index (%) | Hausner's Ratio | Angle of Repose (degree) |
|--------|------------------|-------------------|---------------------|------------------|-----------------|--------------------------|
| 1.     | F-1              | 0.593             | 0.735               | 19.32            | 1.24            | 31.42                    |
| 2.     | F-2              | 0.635             | 0.771               | 17.64            | 1.21            | 33.70                    |
| 3.     | F-3              | 0.639             | 0.729               | 12.35            | 1.14            | 27.44                    |
| 4.     | F-4              | 0.633             | 0.721               | 12.21            | 1.14            | 25.35                    |
| 5.     | F-5              | 0.640             | 0.720               | 11.11            | 1.13            | 27.69                    |

**Preparation of sample solution:**

One tablet equivalent to 52.5mg of Metoprolol succinate was taken in 100ml volumetric flask and 70ml of methanol was added and sonicated for 30min and volume was made up with methanol. From this 10ml of above solution was pipetted out in to 50ml volumetric flask and volume was made up with mobile phase.

**System suitability:**

% RSD of five replicate injections peak should not be more than 2.0%. The

theoretical plate for Metoprolol Succinate and Hydrochlorothiazide peaks should not less than 1500. The tailing factor Metoprolol Succinate and Hydrochlorothiazide peaks should not more than 2.0.

**Procedure:**

20 micro liters of filtered portion of the standard solution and sample solution was injected in to HPLC system. The

chromatogram was recorded and responses were measured for the major peaks.

### **INVITRO DISSOLUTION STUDIES BY HPLC<sup>4,5</sup>:**

#### **Dissolution for Metoprolol Succinate:**

Six tablets of Metoprolol and Hydrochlorothiazide (Bilayer tablets) were placed in the apparatus of USP II (paddle). The medium used was 500 ml of pH 6.8 phosphate buffer solutions and the dissolution mediums were maintained at the temperature of  $37.5 \pm 0.5^{\circ} \text{C}$  the RPM was fixed in 50 RPM. The sample was withdrawn at of 1<sup>st</sup>, 4<sup>th</sup>, 8<sup>th</sup> and 20<sup>th</sup> hr time interval. The estimation was carried out by HPLC method.

#### **Standard preparation:**

Accurately weighed 23.5mg of Metoprolol succinate was taken in 50ml of volumetric flask and 25ml of diluents were added and sonicated to dissolve and the volume was made up with diluents. From this 5ml was pipetted out in to 50ml volumetric flask and volume was made with a diluents. Filtered through 0.45 micron membrane filter.

#### **Sample preparation:**

The dissolution parameters were setted and one tablet is placed in each basket and care was taken to exclude air bubbles from the surface of the tablets and immediately the

apparatus was started after 1<sup>st</sup> hour, 10ml of the sample was withdrawn and filter through whatmann filter paper, 10ml of solution was replaced in to dissolution medium, the same procedure was repeated at 4<sup>th</sup>, 8<sup>th</sup> and 20<sup>th</sup> hour.

#### **Procedure:**

20 micro liters of filtered portion of the standard and sample solution was injected in to HPLC system. The chromatogram was recorded and responses were measured for major peaks.

#### **Dissolution for Hydrochlorothiazide:**

Six tablets of Metoprolol and Hydrochlorothiazide (bilayer tablets) were placed in the apparatus of USP I (Basket). The medium used was the 900 ml of 0.1N Hydrochloric acid solutions and the dissolution mediums maintained at the temperature of  $37.5 \pm 0.5^{\circ} \text{C}$  the RPM was fixed in 100 RPM. The sample withdrawal time of 1hr (60 min). The estimation was carried out by HPLC method.

#### **Standard preparation:**

Accurately weighed 12.4mg of Hydrochlorothiazide was taken in 200ml volumetric flask and 50ml of diluents, kept warm at  $50^{\circ} \text{C}$  in water bath for 20mins to dissolve and volume was made up by the diluents. From this 5ml was pipetted out in

to 100ml volumetric flask and volume was made up with dissolution medium.

### Sample preparation

The dissolution parameters were setted and one tablet was placed in to each basket care was taken to exclude air bubbles from the surface of the tablets and immediately the apparatus was started, after 60<sup>th</sup> min the sample was withdrawn by using whatmann filter.

### Procedure

100 micro liters of filtered portion of the standard and sample solution was injected in to HPLC system. The chromatogram was recorded and the responses were measured for the major peaks.

### Stability Studies<sup>7,8</sup>:

The tablets were packed in blister packing and kept for 60 days at 40°C / 75% RH and 25°C / 60% RH in a stability chamber (Oswald, Mumbai).After 2 months the tablets were withdrawn and evaluated for appearance, average weight, assay and in vitro drug release.

### Kinetic Studies<sup>9</sup>:

The following plots were made: cumulative % drug release vs. time (zero order kinetic model); log cumulative of % drug remaining vs. time (first order kinetic model); cumulative % drug release vs. square root of time (higuchi model). The

regression coefficient R<sup>2</sup> value nearer to 1 indicates the model best fits the release mechanism.

**Table: 5 USP limits for drug release for Metoprolol Succinate SR**

| Time                  | Amount of drug release |
|-----------------------|------------------------|
| 1 <sup>st</sup> hour  | NMT 20%                |
| 4 <sup>th</sup> hour  | 20 – 40%               |
| 8 <sup>th</sup> hour  | 40 – 60%               |
| 20 <sup>th</sup> hour | NLT 80%                |

### RESULTS AND DISCUSSION:

In formulation F-1 to F-5 the SR layer consists of HPMC K100M and HPMC K4M in the concentration of 20% to 50% and 2% to 5% with respect to the average weight and the weight of the tablet was balanced with Micro crystalline cellulose PH101. The release of the drug in F-1 to F-5 was not found to be within the internal specification limit. Therefore the release of the drug was more than the limit. The drug release at 4<sup>th</sup> hour was crossing the limit.

In the formulation F-2, F-3, F-4 and F-5 starch plain was used as a binder in the concentration of 4% to 12% and lubricant concentration is 0.4 to 0.8% respectively to meet the compression and dissolution profile of Hydrochlorothiazide with the specification limit. At the end of 60 min, the release profile of Hydrochlorothiazide in the formulation F-2, F-3, F-4 and F-5

was found to 82.33%, 85.72%, 89.50% and 95.4% respectively. Among these four trials F-5 was found to be satisfactory and it was selected as an immediate release layer to formulate with the sustained release layer of Metoprolol Succinate as a Bilayer tablet.

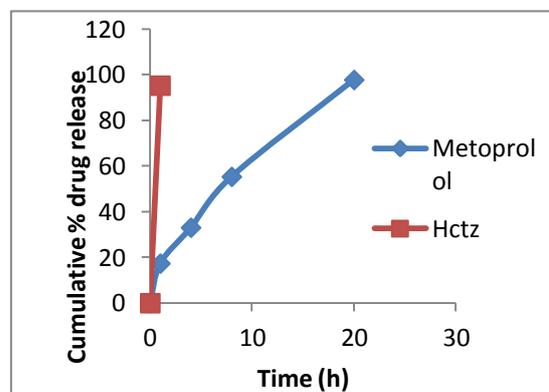
In the formulation F-7 to increase the release of the drug, the concentration of HPMC K100M was increased to 1.5% was found to be satisfactory where the drug release of Metoprolol succinate at 1<sup>st</sup>, 4<sup>th</sup>, 8<sup>th</sup> and 20<sup>th</sup> hour was found to be, 17.34, 33.06, 55.35, and 97.78% respectively. The release of Hydrochlorothiazide at the end of 1 hour was found to be 95.29%.

In formulation F- 8 after stability study at 40<sup>0</sup>C±2<sup>0</sup>C /75%±5% RH after 30 and 60 days. The drug release of Metoprolol Succinate at 1<sup>st</sup>, 4<sup>th</sup>, 8<sup>th</sup> and 20<sup>th</sup> h was found to be 17.30%, 33.04%, 55.68%, 97.76% and 17.33%, 32.72%, 55.30% and 97.64% respectively. The release of Hydrochlorothiazide at the end of 1hr was found to be 95.28 % and 95.19%.

In formulation F- 9 after stability study at 40<sup>0</sup>C±2<sup>0</sup>C /75%±5% RH after 30 and 60 days. The drug release of Metoprolol Succinate at 1<sup>st</sup>, 4<sup>th</sup>, 8<sup>th</sup> and 20<sup>th</sup> h was found to be 17.32%, 33.04%, 55.34%, 97.76% respectively and 17.22%, 33.05%, 55.28% and 97.61% respectively. The

release of Hydrochlorothiazide at the end of 1hr was found to be 95.12 % and 95.23 %.

#### **In-vitro dissolution profile of formulation F-7**



#### **Release kinetics study for optimized Bilayer tablet:**

The kinetics of drug release was determined based on korsmeyer-peppas equation obtained by *in vitro* dissolution data to various kinetics models. Accordingly the R<sup>2</sup> value was found to 0.981 for zero order, 0.966 for first order, 0.996 for Higuchi, 0.998 for korsmeyer-peppas plot. The R<sup>2</sup> value of korsmeyer-peppas was close to 1 and n value was found to be 1.4. Hence the release kinetics was fitted to korsmeyer-peppas equation follows non-fickian diffusion model, and the mechanism of drug release is regarded as super case II transport.

**Table: 6 Release Kinetics**

| Release Kinetics | R <sup>2</sup> |
|------------------|----------------|
| Zero order       | 0.981          |
| First order      | 0.966          |
| Higuchi          | 0.996          |
| Korsmeyer-peppas | 0.998          |

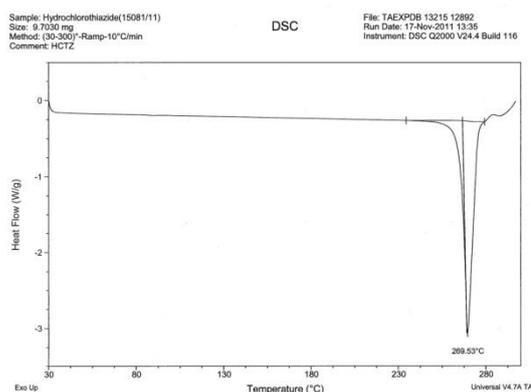
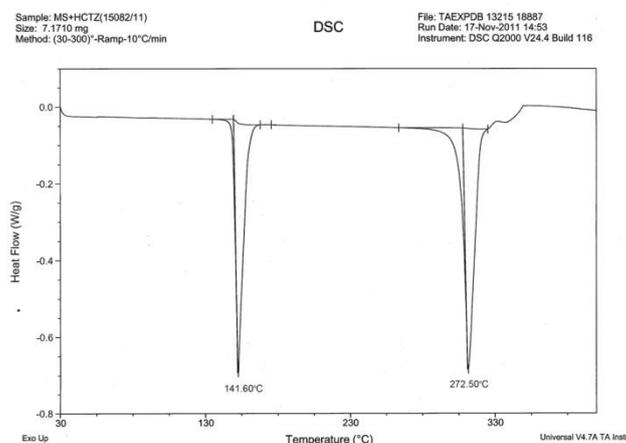
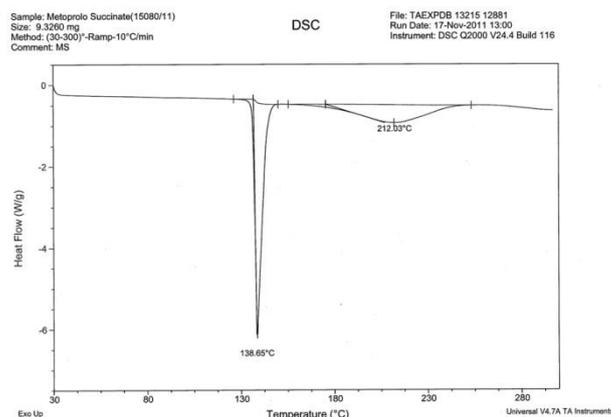
**DSC Studies<sup>13, 14</sup>:**

DSC curves showed that there was no any incompatibility between Metoprolol succinate and Hydrochlorothiazide. In the combination DSC, one peak was obtained at 141.60°C for Metoprolol succinate and another at 272.50 °C for Hydrochlorothiazide. In the individual DSC studies of the drugs, Metoprolol succinate peak was obtained at 138.65 °C and Hydrochlorothiazide peak at 289.53°C. These peaks match the peaks reported in the literature for pure drugs.

**CONCLUSION:**

The present research was carried out to develop a bilayer tablet of Metoprolol Succinate using hydrophilic matrix formers such as HPMC K100M and

HPMC K4M for the sustained release.



layer. Starch is used as a binder for immediate release layer of Hydrochlorothiazide. Combination of Metoprolol Succinate and Hydrochlorothiazide are indicated for the

treatment and relief of Antihypertensive agent Tablet formulation (F-7) showed acceptable pharmacotechnical properties and complied with the internal specification for weight variation, thickness, hardness, friability, drug content and *in vitro* drug release. Drug release from the matrix was found to decrease with increase in polymer concentration in intra and extra granulation, where the polymer concentration was employed from 20-50% w/w of the average tablet weight. However, HPMC 4M required to channelize the drug release was optimized with 2% to 5%. Similarly starch with 12% w/w optimized from 4% onwards, as binder to compress IR layer and dissolution within 60 minutes (internal specification). Reproducibility was checked by intra batch variability study and found no pronounced variation was observed.

The optimized bilayered tablets followed Korsmeyer-peppas kinetic and showed no significant change in physical appearance, drug content or *in vitro* dissolution pattern after storage at 40°C/75%RH for 2 months. Hence, it is finally concluded that, the Bilayer tablet technology can be successfully applied for sustained release of Metoprolol Succinate and immediate-release of Hydrochlorothiazide.

## REFERENCE

1. Lachman L, Liberman H, Kanig J., The theory and practice of industrial Pharmacy, Varghese Publishing House, Mumbai , 3rd edition, 1987, 171-195, 293-345.
2. N.H.Indurwade, T.H.Rajyagures, Nakhat P.D., *Indian Drug* 2002, 39(8) 405-409.
3. Miyazaki S, Kawasaki N, Nakamura T, Iwatsu M, Hayashi T, Hou W M, Attwood D, Oral mucosal bioadhesive tablets of pectin and HPMC: *invitro* and *in vivo* evaluation. *International Journal of Pharmaceutics*, 2000, 204, 127–132.
4. jay L. Barhate, Santosh N. Shinde, Monali S. Sali, Kunal D. Ingale, Vishnu P. Choudhari, Bhanudas S. Kuchekar, Fabrication of Controlled Release Metoprolol Succinate Matrix Tablet : Influence of Some Hydrophilic Polymers on the Release Rate and *In Vitro* Evaluation, *International journal of pharma world research*, 2010, 2 (1),
5. U.S. Pharmacopeia 2007, USP 30 NF 25 2963- 2966.
6. Indian Pharmacopoeia 2010, (2):2566-2568.

7. Rakhee .A. Surana, Anand S. Surana, A.V. Chandewar, S. B. Jai swal, Formulation development and evaluation of phenylpropanolamine hydrochloride sustained release pellets: effect of different solvent used for coating solution on the release process, *Journal of Pharmacy Research* **2011**,4(8),2831-2835.
8. C.T.Rhodes, T.Cartesan, Drug stability principle and procedure, 3<sup>rd</sup> edition,. New York, **2001**, 21-46.
9. Martin.A, Bustamante.P, and Chun.A, physical pharmacy-physical chemical principles in the pharmaceutical sciences, 4<sup>th</sup> ed., Lipincott Williams and Wilkins, Baltimore **2002**, 446-448.
10. Fridrun Podczecka, Emad Al-Mutib the tensile strength of bilayered tablets made from different grades of microcrystalline cellulose. *European Journal of Pharmaceutical Sciences*, **2010**, 41, 483–488.
11. Singh Brijesh, D.K Patel and S.K Ghosh, Development of Reverse-Phase HPLC Method for Simultaneous Analysis of Metoprolol Succinate and Hydrochlorothiazide in a Tablet Formulation, *Tropical Journal of Pharmaceutical Research*, December **2009**, 8 (6), 539-543.
12. . CH.M.M. Prasada Rao , S.A.Rahaman ,Y.Rajendra Prasad , P. Gangi Reddy, RP-HPLC method of simultaneous estimation of Amlodipine Besylate and Metoprolol in combined dosage form, *International journal of pharma.Research and Development*, **2010**, 2(9) 69-76.
13. . S. Jayaprakash, S. Mohamed Halith, K.Kulathuran Pillai, Priya Balasubramaniam, P.U. Mohamed Firthouse, M .Boopathi, Formulation and evaluation of bilayer tablets of amlodipine besilate and metoprolol succinate, *Scholars Research Library Der Pharmacia Lettre*, **2011**, 3 (4), 143-154.
14. M .Paneerselvam, R.Natarajan, S.Selvarajan and N.N.Rajendran. A Novel drug-drug solid dispersion of Hydrochlorothiazide Losartan Potassium, *International Journal of Pharma and Bio Sciences*, **2010**, 1(4), 68-80.