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# DESIGN AND DEVELOPMENT OF METOPROLOL SUSTAINED RELEASE MICROSPHERES

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## ABSTRACT

The study was aimed to Formulate Metoprolol sustained release microspheres. Microspheres were prepared by Ionic-Gelation method using Hydroxy Propyl Methyl Cellulose (HPMC), Eudragit S100and Ethyl cellulose for sustained release in view to prolong drug release. Metoprolol is an adreno receptor beta blocking agent used in the treatment of hypertension. It belongs to BCS class I drug means having high solubility and high permeability. Its biological half life ranges from 3 to 7 hours & oral bioavailability is 50% hence requires frequent oral administration for adequate treatment of hypertension. Conventional dosage form administration of Metoprolol has been reported to exhibit fluctuations in plasma drug levels resulting in either manifestation side effects or reduction in drug concentration at receptor site. Hence oral sustained dosage form of microspheres was developed. The microspheres were evaluated for various characteristics like encapsulation efficiency, percentage yield, partial size and the In vitro release. The Microspheres were found to be spherical, free-flowing, uniform in size and the microencapsulation efficiency was in the range of 87.4%.

**KEYWORDS:** Microspheres, Hypertension, Metoprolol, Sustain release.

## INTRODUCTION

Oral drug delivery system has been known for decades as the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drugs.[1]

Sustained release, sustained action, prolonged action, controlled release, extended released, depot release are the terms used to identify drug delivery systems that are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose of drug. Microspheres are one of the approaches to release the drug for prolonged period.[2-5]

Microspheres are small spherical particles, with diameters in the micrometer range (typically 1 µm to 1000 µm (1 mm)). Microspheres are also known as microparticles.[6,7]

## MATERIALS AND METHODS

### MATERIALS

Metoprolol was a gift from Yarrow chem. Mumbai, Ethyl cellulose was obtained from Ases chemical lab. HPMC, Hydrochloric acid, and Sodium Alginate from Loba chemie Pvt Ltd., Eudragit S100 from Chemdyes corporation. Calcium chloride from Sd Fine Chem Ltd, Mumbai. All chemicals and reagents used were of analytical.

### Drug profile

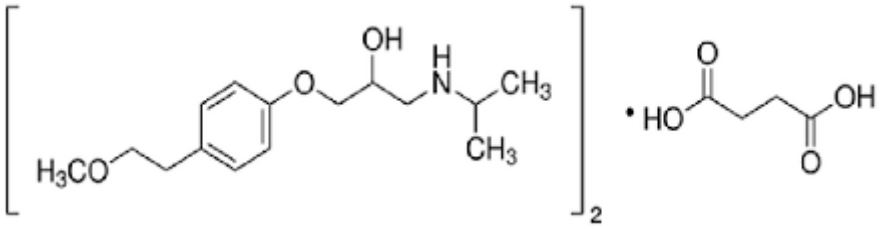
**Metoprolol succinate**[8]

**Chemical Name:** 1-[4-(2-Methoxyethyl)phenoxy]-3-[(propan-2-yl)amino]propan-2-ol

**Systematic (IUPAC) Formula**: C15H25NO3

**Molecular Weight:** 267.364 g/mol

**Structure**



**Description**
Metoprolol hydrochloride is a stable, white, crystalline solid which is readily soluble in water and ethanol.

**Physico-chemical Properties**
**Melting point:** 120 °C (248 °F)
**Solubility:** soluble in water and alcohol; slightly soluble in chloroform; practically insoluble in ether.
**Spectral Properties:** λmax (Metoprolol): 296nm.

**METHODS**
The following steps are involved in preparation of microspheres.
1. Prepare Polymer Solution by dissolving polymer in distilled water.
2. Dissolve Drug in the above Solution.
3. Sonicate the Drug-Polymer Solution for proper mixing.
4. Above solution was added drop by drop through hypodermic needle into 50ml of 5% w/v CaCl2 solution.
5. Formed Metoprolol Microspheres were stirred in the cross linking agent for 1hr at 100rpm.
6. Wash the Microspheres with de-ionized water and dried at 80°C for about 2 hour.
7. Transfer prepared Microspheres to desiccators to maintain the constant Humidity conditions.
All Formulations were prepared by Ionic Gelation method using different polymers were given in table 1.

**CHARACTERIZATION OF MICROSPHERES**
**Particle size analysis:** All the microspheres were evaluated with respect to their size using optical microspheres fitted with an ocular micrometer and a stage micrometer. The size more than 50 microspheres was measured randomly by optical microscope. The average particle size of microspheres was determined by the total size of the microspheres divided by the number of microspheres.[9] Least count of the ocular micrometer was calculated by the following formula:

$$\text{Least count} = \frac{\text{No of Division of Stage Micrometer}}{\text{No of Division of Ocular Micrometer}} X\ 100$$

**Particle Morphology**: The shape and surface morphology of microsphere samples were observed under SEM. The microsphere photographs of suitable magnification were obtained for surface topography.[10]

**Determination of encapsulation efficiency:** Drug entrapment efficiency of Metoprolol microspheres was performed by accurately weighing 50 mg of microspheres and crushing them properly in a glass mortar and pestle. These weighed microspheres were suspended in 50 ml of hydrochloric acid buffer (pH 1.2) and it was kept aside for 24 hours. There after suitable dilution, drug content in the filtrate was analyzed spectrophotometrically at 296 nm using U. V. spectrophotometer.[11]

$$\%\ \text{Encapsulation efficiency} = \frac{\text{Actual content}}{\text{Theoretical content}} X100$$

**In vitro drug release studies:** The drug release studies were carried out using six basket dissolution apparatus USP type II. The microspheres were placed in a non-reacting mesh that had a smaller mesh size than the microspheres. The mesh was tied with a nylon thread to avoid the escape of any microspheres. The dissolution medium used was 900 ml of 0.1 N hydrochloric acid at 37°C. At specific time intervals, at hourly intervals up to 12 hrs. 5 ml aliquots were withdrawn and analyzed by UV spectrophotometer at 296 nm after suitable dilution. The withdrawn volume was replaced with an equal volume of fresh 0.1 N hydrochloric acid.[12]

**Stability studies**: Stability studies were carried out as per ICH guidelines. The microspheres were placed in a screw capped glass containers and stored at 25 ± 2°C (Room temperature), 2 to 8°C (Refrigeration temperature), 45°C for a period of 30 days.[13]

**RESULTS AND DISCUSSION**
**Particle size analysis and Particle Morphology**
The shape, size of microspheres prepared by using different polymers were identified and shown in Fig:1 and table 2.

**Determination of encapsulation efficiency:** Drug entrapment efficiency of Metoprolol microspheres was tabulated in table3.

***In vitro* drug release**
At the end of 12 hrs the percentage cumulative release of Metoprolol from HPMC microspheres were found to be 82.5%, 80.2%, 75.2% for formulations F1, F2, F3 respectively. The percentage cumulative drug release from Eudragit S100 microspheres were found to be 91.4%, 83.9%, 82.5% for formulations F4, F5, F6 respectively. The percentage cumulative drug release for Ethyl cellulose microspheres were found to be 81.5%, 80.2%, 78.5% for formulations F7, F8, F9 respectively. It is observed that the percentage cumulative amount of

drug release decreased as the concentration of polymer increase. The cumulative percentage drug release for Eudragit S100 microspheres was found to be maximum followed by HPMC microspheres, followed by Ethyl cellulose microspheres (Fig: 2-5 and Table 4).

**Stability study**

From the stability studies of formulation F4 it was observed that no significant change in drug loaded microspheres stored at 25 ± 2°C (Room temperature), 2 to 8°C (Refrigeration temperature), 45°C for a period of 30 days (Table 5; Fig: 6).

**Table 1: Formulation table for Metoprolol microspheres.**

| S.NO | FORMULATION CODE | Drug (mg) | POLYMER | POLYMER RATIO | Calcium chloride (%w/v) | Sodium Alginate (mg) |
|---|---|---|---|---|---|---|
| 1 | F1 | 100 | HPMC | 1:1 | 5 | 1000 |
| 2 | F2 | 100 | HPMC | 1:2 | 5 | 1000 |
| 3 | F3 | 100 | HPMC | 1:3 | 5 | 1000 |
| 4 | F4 | 100 | Eudragit S100 | 1:1 | 5 | 1000 |
| 5 | F5 | 100 | Eudragit S100 | 1:2 | 5 | 1000 |
| 6 | F6 | 100 | Eudragit S100 | 1:3 | 5 | 1000 |
| 7 | F7 | 100 | Ethyl Cellulose | 1:1 | 5 | 1000 |
| 8 | F8 | 100 | Ethyl Cellulose | 1:2 | 5 | 1000 |
| 9 | F9 | 100 | Ethyl Cellulose | 1:3 | 5 | 1000 |

**Table 2: Particle size determination.**

| CODE | Mean Particle Size (µm) |
|---|---|
| F1 | 293.50 ± 0.707 |
| F2 | 302.85 ± 0.636 |
| F3 | 309.63 ± 0.042 |
| F4 | 344.70 ± 3.818 |
| F5 | 360.75 ± 5.303 |
| F6 | 382.50 ± 5.091 |
| F7 | 252.45 ± 0.636 |
| F8 | 253.80 ± 1.273 |
| F9 | 279.00 ± 1.273 |

**Table 3: Percentage encapsulation efficiency.**

| CODE | Encapsulation efficiency (%) |
|---|---|
| F1 | 76.4% |
| F2 | 82.6% |
| F3 | 79.6% |
| F4 | 87.4% |
| F5 | 84.6% |
| F6 | 81.6% |
| F7 | 75.4% |
| F8 | 84.2% |
| F9 | 82.4% |

**Table 4: In vitro drug release study.**

| Time (h) | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 1.08 | 1.02 | 1.02 | 1.9 | 1.51 | 1.32 | 1.04 | 1.02 | 1.01 |
| 2 | 2.27 | 2.03 | 2.01 | 3.1 | 2.8 | 2.72 | 2.21 | 2.18 | 2.16 |
| 3 | 4.42 | 3.56 | 3.41 | 5.2 | 4.2 | 3.15 | 3.15 | 3.12 | 3.05 |
| 4 | 8.61 | 7.54 | 6.21 | 9.2 | 7.9 | 5.2 | 7.45 | 6.85 | 5.47 |
| 5 | 14.1 | 13.2 | 11.0 | 15.2 | 14.2 | 13.5 | 12.5 | 11.5 | 10.5 |
| 6 | 22.1 | 21.1 | 20.5 | 25.1 | 19.5 | 17.2 | 20.4 | 19.5 | 17.5 |
| 7 | 32.1 | 30.1 | 30.5 | 33.1 | 30.5 | 30.4 | 28.5 | 26.4 | 23.4 |
| 8 | 43.2 | 41.8 | 41.2 | 48.2 | 42.8 | 41.8 | 41.2 | 35.2 | 34.2 |
| 9 | 57.2 | 55.8 | 51.0 | 61.2 | 57.2 | 57.1 | 52.2 | 45.2 | 45.2 |
| 10 | 63.2 | 59.2 | 55.8 | 69.1 | 65.8 | 62.1 | 60.2 | 54.2 | 51.2 |
| 11 | 71.2 | 70.2 | 68.5 | 76.1 | 71.5 | 70.1 | 69.2 | 68.5 | 67.2 |
| 12 | 82.5 | 80.2 | 75.2 | 91.4 | 83.9 | 82.5 | 81.5 | 80.2 | 78.5 |

**Table 5: Stability studies of selected formulation F4.**

| Time (Days) | % Drug Content | | |
|---|---|---|---|
| | 4°C | 25°C | 45°C |
| 0 | 100 | 100 | 100 |
| 15 | 100 | 100 | 99.52 |
| 30 | 99.75 | 99.49 | 98.89 |

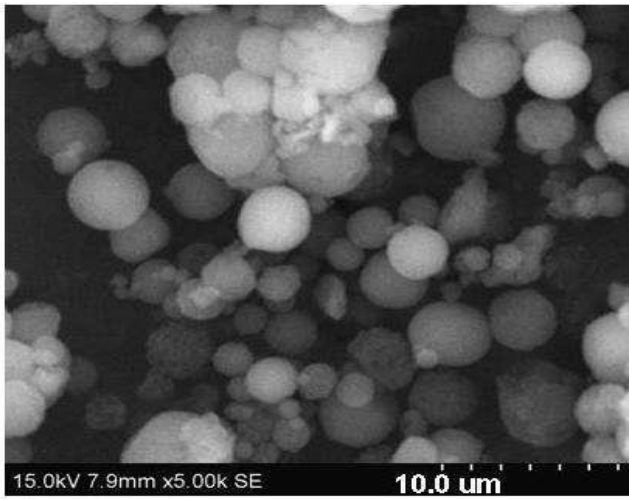



**Figure 1: (A) Ethyl cellulose microspheres.**


**Figure 1: (B) Eudragit S100 microspheres.**


**Figure 1: (C) HPMC microspheres.**

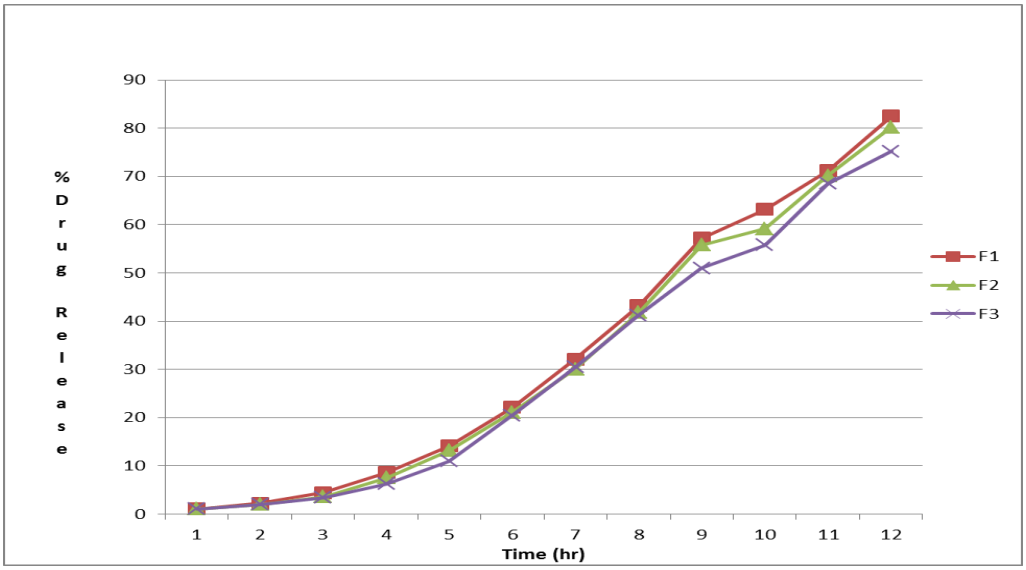



**Fig 2: Comparative drug release of F1,F2 and F3.**

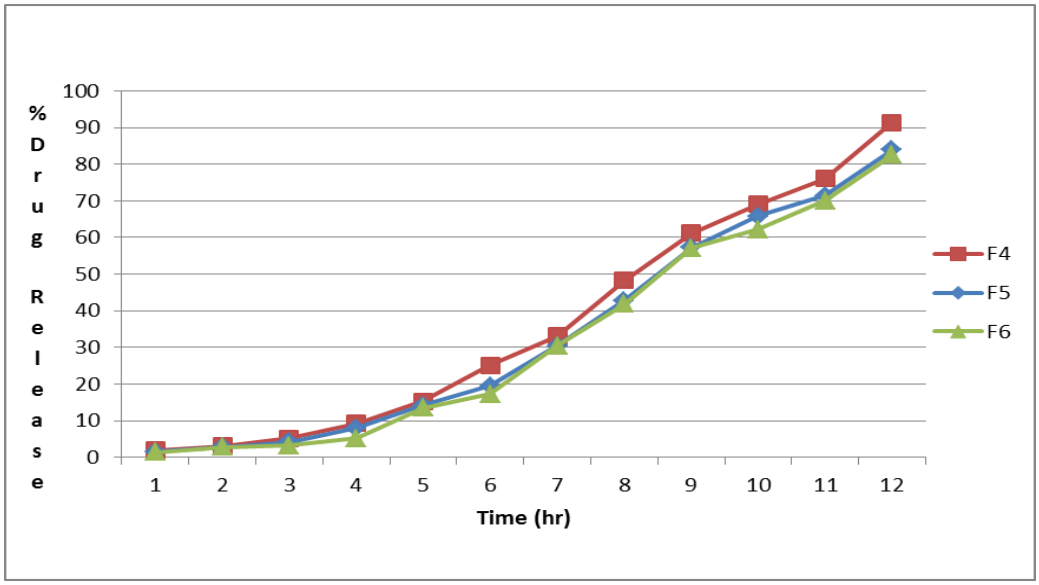



**Fig 3: Comparative drug release of F4,F5 and F6.**

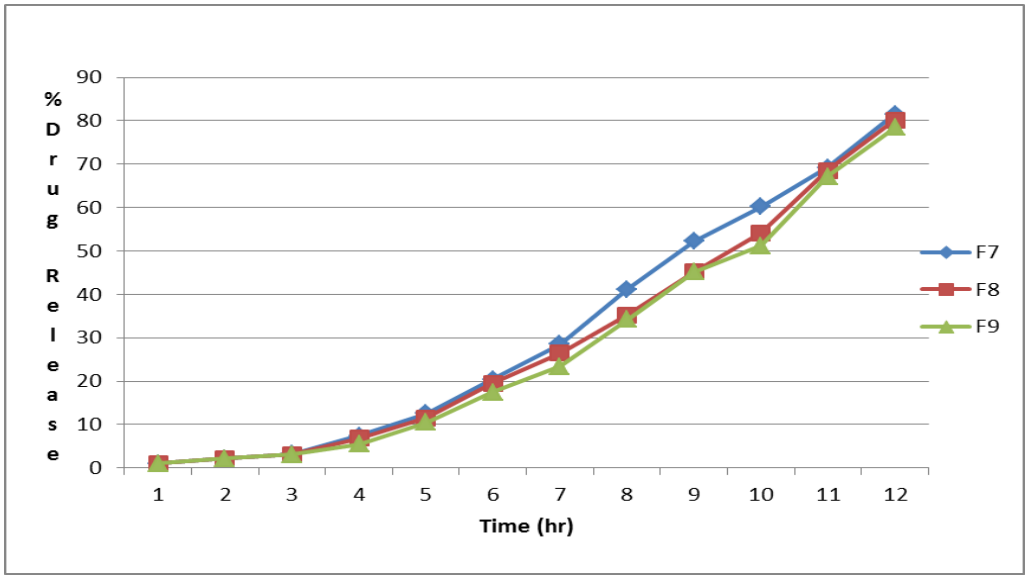



**Fig 4: Comparative drug release of F7,F8 and F9.**

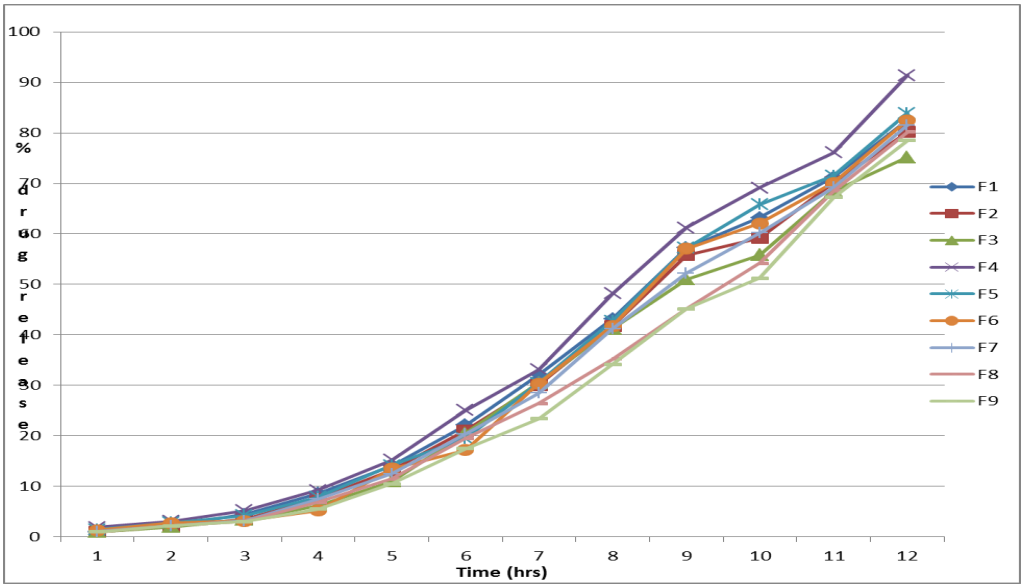



**Fig 5: Comparative drug release of formulations F1 to F9.**

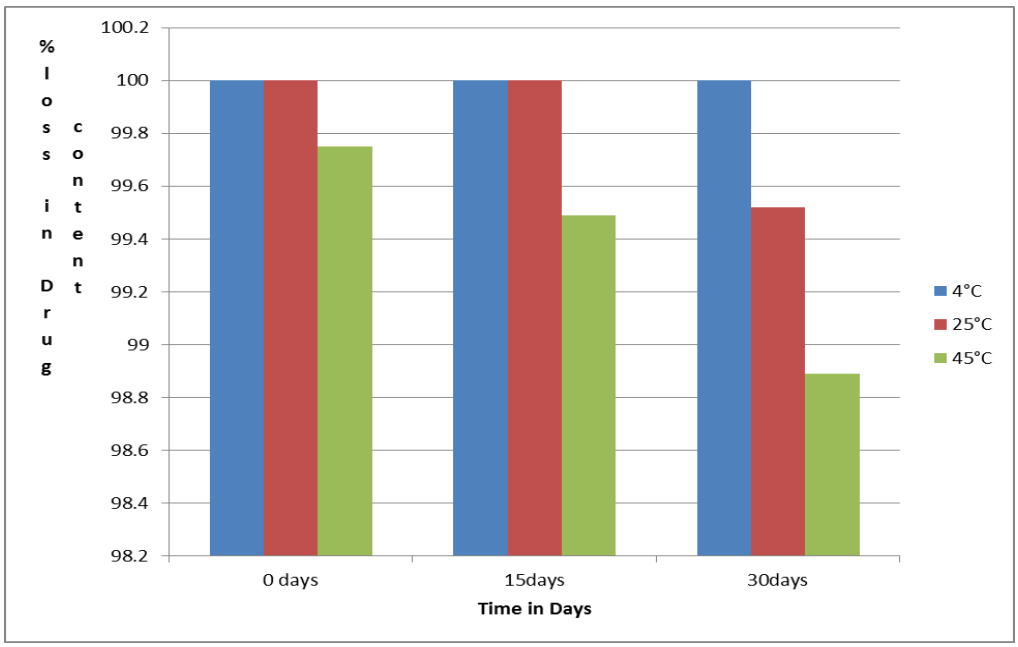



**Figure 6: Stability studies of formulation F4.**

## CONCLUSION

The incorporation of the highly water soluble Metoprolol was done using ethylcellulose, Eudragit S100 and HPMC as the polymer. The formulations exhibited sufficient encapsulation effeciency and it was seen that with the increase in concentration of polymer decreased the particle size and cumulative% drug release. Percentage drug release study was affected by the polymer concentration.

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