ABSTRACT
Formulated Metoprolol sustained release microspheres. Microspheres are prepared by Ionic-Gelation method using Hydroxy Propyl Methyl Cellulose (HPMC), Ethyl cellulose and Sodium CMC for sustained release in view to prolong drug release. Metoprolol is an adreno receptor beta blocking agent used in the treatment of hypertension and characterized by high solubility and high permeability which corresponds to BCS class I drug. Plasma half life ranges from 3 to 7 hours & oral bioavailability is 50% hence require frequent oral administration for adequate treatment of hypertension. Administration of conventional tablet of Metoprolol has been reported to exhibit fluctuations in plasma drug levels resulting in either manifestation of side effects or reduction in drug concentration at receptor site. so that oral sustained dosage form was developed. The microspheres were evaluated for various characteristics like encapsulation efficiency, percentage yield, partial size and the In vitro release for 12 hours. The Microspheres were found to be discrete, spherical, and free-flowing. The microspheres were uniform in size, and the microencapsulation efficiency was in the range of 91.7%. Microspheres had good spherical geometry.

Keywords: Microspheres, Hypertension, In vitro release, Encapsulation efficiency

INTRODUCTION
Oral Drug Delivery System

Oral drug delivery 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 via various pharmaceutical products of different dosage forms.

Sustained Release Drug Delivery

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

Microspheres are small spherical particles, with diameters in the micrometer range (typically 1 μm to 1000 μm (1 mm)). Microspheres are sometimes referred to as microparticles.

DRUG PROFILE
METOPROLOL SUCCINATE
Chemical Name: 1-[(2-Methoxyethyl)phenoxy]-3-[(propan-2-ylamino)propan-2-ol
Systematic (IUPAC) Formula: C_{15}H_{25}NO_{3}
Molar. Mass: 267.364 g/mol

STRUCTURE

Figure 1: Structure of Metoprolol hydrochloride
Description
Metoprolol hydrochloride is a stable, white, crystalline solid which is readily soluble in water and ethanol. Its molecular weight is 267.364 g/mol

Physico-chemical Properties:
Melting point: 120 °C (248 °F)
Solubility: soluble in water, and alcohol; slightly soluble in chloroform; practically soluble in ether. As for acid, alkali or organic solvent like diethyl ether.

Spectral Properties: \( \lambda_{\text{max}} \) (Metoprolol): 296.

FORMULATION OF SUSTAINED RELEASE MICROSPHERES\(^3,4,5\)

**PROCEDURE:** The following steps involved in preparation of Metoprolol microspheres.
1. Preparation of Polymer Solution by dissolving in distilled water.
2. Dissolve Drug (Metoprolol) in above Solution.
3. Sonicate the Drug-Polymer Solution for proper mixing.
4. Above solution was added drop wise by a 26G hypodermic needle into 50ml of 5% w/v CaCl\(_2\) solution.
5. Formed Metoprolol Microspheres were stirred in the crosslinking agent for 1hr at 100rpm.
6. Wash the Microspheres with de-ionized water and dried at 80°C for 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.

Table No. 2: Trail formulations composition

<table>
<thead>
<tr>
<th>Trail Formulations</th>
<th>Metoprolol (mg)</th>
<th>HPMC K100M (mg)</th>
<th>Sodium CMC (mg)</th>
<th>Ethyl Cellulose (mg)</th>
<th>Sodium Alginate (mg)</th>
<th>CaCl(_2) (% W/V)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>100</td>
<td>50</td>
<td>100</td>
<td></td>
<td>1000</td>
<td>5</td>
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<tr>
<td>F2</td>
<td>100</td>
<td>100</td>
<td>150</td>
<td></td>
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<td>5</td>
</tr>
<tr>
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<td>200</td>
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<tr>
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<td>100</td>
<td>150</td>
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<td>1000</td>
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</table>

RESULTS AND DISCUSSIONS

**PREFORMULATION STUDIES\(^8,9\)**
Drug excipient compatibility studies
The compatibility of drug and formulation components is important prerequisite before formulation. It is therefore necessary to confirm that the drug does not react with the polymers and excipients under experimental conditions and affect the shelf life of product or any other unwanted effects on the formulation.

The compatibility study between the drug and the polymer was done by I.R studies. No major peak shift was observed in the I.R graphs in major functional groups. Based on the compatibility studies obtained by I.R studies, polymers, HPMC,EC,Sod.CMC were taken for the optimization of the formulation, which is compatible with the drug.

**EVALUATION TESTS\(^14,17,18\)**

**PARTICLE SIZE**

SEM photograph of formulated Microspheres

**IN-VITRO DISSOLUTION DATA: DISSOLUTION KINETICS**

Table 4: Percentage drug release for optimized formulation

<table>
<thead>
<tr>
<th>Time(hours)</th>
<th>Absorbance</th>
<th>% Cumulative drug release</th>
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<tr>
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<td>2</td>
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<tr>
<td>3</td>
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<tr>
<td>4</td>
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<td>56.2</td>
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<tr>
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<tr>
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<tr>
<td>12</td>
<td>0.692</td>
<td>96.8</td>
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</table>
Figure 4: Dissolution profile of formulation F-5

**COMPARATIVE DISSOLUTION PROFILE**

Table 5: Comparative dissolution profile for different formulations F1-F5

<table>
<thead>
<tr>
<th>Time (hours)</th>
<th>F-1 % CDR</th>
<th>F-2 % CDR</th>
<th>F-3 % CDR</th>
<th>F-4 % CDR</th>
<th>F-5 % CDR</th>
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<td>96.8</td>
</tr>
</tbody>
</table>

**Figure 5: Comparative dissolution profile for formulation F1-F5.**

**Inference:** From the above fig the dissolution profile for the formulation F-5 was found to be have the more cumulative % drug release.
ZERO ORDER PLOT

![Zero order plot for optimized formulation F-5](image)

**Figure 6: Zero order plot for optimized formulation F-5**

FIRST ORDER PLOT

![First order plot for optimized formulation F-5](image)

**Figure 7: First order plot for optimized formulation F-5**

**Inference:** From the above graph $R^2$ value is (0.931) and for zero order plot $R^2$ value is (0.919) which indicates that the order of release was first order.

HIGUCHI’S PLOT

![Higuchi’s plot for optimized formulation F-5](image)

**Figure 8: Higuchi’s plot for optimized formulation F-5**
KORSEMEYER-PEPPAS PLOT

Inference: As per the above plot the R2 value for Higuchi (0.919) and for Korsemeyer – peppas plot (0.961), showing that the mechanism of drug release from the formula was found to be diffusion controlled release.

Stability studies

The accelerated stability study for the formulation at 40 ± 2°C and 75 ± 5 % RH was conducted for the 6 months, which includes the testing of parameters like identification of physical characters, identified by IR studies, dissolution profile and assay throughout period.

CONCLUSION

Thus, Microspheres with a coat consisting of Sodium alginate and other polymers (Sodium CMC, HPMC K100M and Ethyl Cellulose) could be prepared by an Ionic gelation process. The microspheres exhibited good sustained release in an in vitro test. Metoprolol release from these sustained release microspheres was slow and extended over a longer period of time (12hours) and depended on composition of the coat. Drug release was diffusion controlled and followed zero-order kinetics. In the in vitro evaluation, EC-HPMC K100M microspheres could sustain the drug release over a 12-hour period. Based on results the best formulation F5 can successfully employed as a controlled release drug delivery system. These sustained release microspheres are thus suitable for oral sustained release of Metoprolol.

- FTIR studies revealed no interactions between the drug and polymers used.
- Formulated Microspheres gave satisfactory result for various physico-chemical evaluations like physical appearance, surface morphology, entrapment efficiency, percentage drug loading and in vitro drug release.
- The prepared beads showed required drug release in about 12 hours.
- From the research, it can be concluded that Metoprolol can be formulated as microspheres for the desired use in treatment of Hypertension.

REFERENCES


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