FORMULATION AND EVALUATION OF CONTROLLED RELEASE PELLETS OF METOPROLOL SUCCINATE BY EXTRUSION-SPERONIZATION METHOD

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ABSTRACT
The objective of this study was to prepare and evaluate controlled release pellets of Metoprolol Succinate by using Extrusion-Spheronization Method. The different formulations were prepared using Eudragit L, Ethyl Cellulose as hydrophobic polymer, MCC PH 101 as a Spheronizing aid and methyl alcohol as a solvent. In vitro drug release study in pH 6.8 phosphate buffer. Stability studies were carried out for a period of 90 days at 40±2 °C and 75±5% RH. The drug content was in the range of 96.09%. The mean particle size of the drug loaded pellets was in the range 96 μm to 1010.21 μm. SEM photographs and calculated sphericity factor confirmed that the prepared formulations were spherical in nature. The compatibility between drug and polymers in the drug loaded pellets was confirmed by DSC and FTIR studies. Stability studies indicated that pellets are stable.

Keywords: Metoprolol succinate, Extrusion-spheronisation method, Ethyl cellulose (EC), Eudragit L, In-vitro study.

INTRODUCTION
Oral route is the most common route of drug administration. Modern drug delivery strategies try to improve oral drug delivery. If patient self-administration cannot be achieved, the sale of drug constitutes only small fraction of what the market would be otherwise. Tablets and capsules represent unit dosage forms in which one usual dose of drug has been accurately placed. Controlled release is a term referred to the presentation or delivery of compounds in response to stimuli or time. Most commonly it refers to time dependent release in oral dose formulations. Timed release has several distinct variants such as sustained release where prolonged release is intended, pulse release, delayed release (e.g. target the different regions of the GI tract) etc. A distinction of controlled release is that not only prolongs action but it attempts to maintain drug levels within the therapeutic window to avoid potentially hazardous peaks in drug concentration following ingestion or injection and to maximize therapeutic efficiency. An ideal drug delivery system should deliver precise amounts of a drug at a preprogrammed rate to achieve a drug level necessary for treatment of the disease. Metoprolol is a beta1-selective adrenergic receptor blocking agent. Metoprolol BCS class I drug i.e. High solubility High permeability. Thus the present study purpose to formulation of Controlled release pellets containing metoprolol.

MATERIAL AND METHODS
Material
Metoprolol Succinate was obtained as a gift sample from Wockhardt, Pharmaceutical Ltd. (Aurangabad, India), Eudragit L, Ethyl Cellulose from Evonik Pharma Ltd. (I), All other chemicals and reagents used were of AR grade.
Method
Metoprolol Succinate controlled release pellets were prepared by Extrusion-spheronization method with Eudragit L and Ethyl Cellulose as controlled release polymer.

**UV-Visible Spectroscopic Scanning- Spectral Analysis**

**Determination of UV Spectrum in Phosphate Buffer pH 6.8**
The stock solution of Metoprolol Succinate (100µg/ml) was prepared by dissolving it in phosphate buffer pH 6.8. A dilution of 20 µg/ml was kept in cuvette of path length 10 mm. The UV spectrum was recorded using double beam UV-VIS spectrophotometer in the wavelength range 200 nm – 400 nm.

**Calibration curve of the drug**

**Preparation of Standard Curve in Phosphate Buffer pH 6.8**
A stock solution of Metoprolol Succinate (100 µg/ml) was prepared by dissolving 10 mg of drug in phosphate buffer pH 6.8 and final volume was made to 100 ml. The solutions in concentration range of 5-30 µg/ml were prepared by appropriate dilutions of stock solution. The UV absorbance of these solutions was determined spectrophotometrically at λ max 222 nm.

**Formulation of Pellets**
Drug Loaded Pellets were prepared by weighing required quantity of Metoprolol Succinate, MCC, Eudragit L, Ethyl Cellulose in methanol. The wet mass was immediately passed through extruder with 1mm sieve. Extrudate so obtained were spheronized in Spheronizer having cross line plate of size 4.2 mm.

### Table 1: Formula as per experimental plan for controlled release polymer

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
<th>F8</th>
<th>F9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metoprolol Succinate</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Eudragit L</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Ethyl cellulose</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>MCC</td>
<td>42</td>
<td>41</td>
<td>40</td>
<td>40</td>
<td>39</td>
<td>38</td>
<td>38</td>
<td>37</td>
<td>36</td>
</tr>
<tr>
<td>Methanol</td>
<td>qs.</td>
<td>qs.</td>
<td>qs.</td>
<td>qs.</td>
<td>qs.</td>
<td>qs.</td>
<td>qs.</td>
<td>qs.</td>
<td>qs.</td>
</tr>
</tbody>
</table>

* All values are in %

**Evaluation of Pellets**
The pellets evaluated for in process quality control test-

**Flow properties of pellets**

**Determination of Bulk Density and Tapped Density**
An accurately weighed quantity of the granules/powder (W) was carefully poured into the graduated cylinder and volume (V0) measured. Then the graduated cylinder was closed with lid and set into the tap density tester (USP). The density apparatus set for 100 tabs and after that the volume (Vf) measured and continued operation till the two consecutive readings were equal.

The bulk density and the tapped density calculated using the following formulae-

**Bulk density** = \( \frac{W}{V_0} \)

**Tapped density** = \( \frac{W}{V_f} \)

Where, \( W \) = Weight of the powder  
\( V_0 \) = Initial volume  
\( V_f \) = final volume

**Compressibility Index (Carr’s Index)**
Carr’s index (CI) is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is.

\[ CI = (TD-BD) \times 100/TD \]
Hausner’s Ratio
It is the ratio of tapped density and bulk density. Generally a value less than 1.25 indicates good flow properties, which is equivalent to 20% of Carr’s index.

Drug Content
Accurately weighed 28 mg of pellets (equivalent to 10 mg. of drug) were crushed in dried mortar pestle. Powder of pellets was dissolved in 100 ml with phosphate buffer pH 6.8. Sample was stirred for 15 min and filtered. Dilutions of solution were prepared and Analyzed by UV-spectrophotometer at 222 nm.

Morphological Characteristic of All Batches
All the factorial batches were studied for morphological features like roundness, aspect Ratio, pellet size, and shape by using photomicrograph.

Friability
Accurately weighed quantity of pellets (3 gm) taken from final batch of pellets and placed in friabilator and tumbled for 100 revolutions at 25 rpm. After friability testing, the pellets were sieved through sieve no. 20. The weight loss (%) was calculated as:

\[ \% \ F = \frac{(W_i - W_r)}{W_i} \times 100 \]

Wi is initial weight of pellets before friability testing, Wr is the weight of pellets retained above the sieve after friability testing.

Scanning Electron Microscopy
Scanning electron microscopy (SEM) is the technique of choice for measuring the shape and surface morphology of pellets.

Drug Excipients Interaction Study
Fourier Transform Infrared Spectroscopy (FT-IR)
It was determined by FT-IR (PRESTIGE-21, Shimadzu). The base line correction was done with blank background measurement. Then the spectrum of dried drug was run. FT-IR spectra were recorded in the wavelength region of 4000 to 500 cm\(^{-1}\).

Differential Scanning Calorimetry (DSC)
The 3.41 mg of sample was weighed and sealed in aluminum pan. Empty aluminum pan was used as a reference. DSC thermogram was recorded.

In-Vitro Drug Release Studies
The in vitro release of the drug from pellets of all formulation batches were performed using USP apparatus Type I (Basket). The dissolution medium consisted of 900 ml of phosphate buffer pH 6.8. Dissolution was performed at \(37\pm0.5^\circ C\), with stirring speed of 50 rpm. 5 ml of aliquot was withdrawn at time intervals of 1, 2, 4, 6, 8, 10, 12 Hrs. The medium was replenished with same amount of fresh dissolution media each time. The filtered samples were analyzed by UV-VIS spectrophotometer at 222 nm and absorbance’s were recorded.

Kinetics of Drug Release
The dissolution profile of all the formulations were fitted to zero order kinetics, first order kinetics, Higuchi, Hixson-Crowell, Korsmeyer and Peppas to ascertain the kinetic modeling of drug release by using a PCP Disso Version 2.08 software, and the model with the higher correlation coefficient was considered to be the best model.
RESULT AND DISCUSSION

UV-Visible Spectroscopic Scanning- Spectral Analysis

**Figure 1:** Wavelength maxima of metoprolol succinate in phosphate buffer pH 6.8 (Conc. 20 ppm)- 222 nm

**Table 2:** Standard calibration curve data for metoprolol succinate in phosphate buffer pH 6.8

<table>
<thead>
<tr>
<th>Conc. (ppm)</th>
<th>Abs. at (222nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.0000</td>
</tr>
<tr>
<td>5</td>
<td>0.2206</td>
</tr>
<tr>
<td>10</td>
<td>0.4167</td>
</tr>
<tr>
<td>15</td>
<td>0.6335</td>
</tr>
<tr>
<td>20</td>
<td>0.8505</td>
</tr>
<tr>
<td>25</td>
<td>1.0646</td>
</tr>
</tbody>
</table>

**Figure 2:** Calibration curve of metoprolol succinate in phosphate buffer pH 6.8 (Linearity of Metoprolol Succinate).

**Drug-Polymer Interaction Study**

**FT-IR**

The drug was found compatible with polymer.

http://www.ijdrt.com
The Thermogram of Metoprolol Succinate showed an endothermic peak at 138.70 °C. with an onset at 137.60°C.
Evaluation of Flow Properties of Pellets

The flow properties of pellets were most important parameter for filling pellets into the capsule shell. The values of angle of repose, Carr’s index and Hausner’s ratio indicate excellent flow properties of pellets. All the factorial batches were evaluated for flow property.

Table 3: Evaluation Parameter of Pellets

<table>
<thead>
<tr>
<th>Batch</th>
<th>Angle of repose (θ)</th>
<th>Bulk density (gm/cm$^3$)</th>
<th>Tapped density (gm/cm$^3$)</th>
<th>Carr’s index (%)</th>
<th>Hausner’s ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>23.56</td>
<td>0.8782</td>
<td>0.92</td>
<td>4.54</td>
<td>1.04</td>
</tr>
<tr>
<td>F2</td>
<td>24.01</td>
<td>0.7745</td>
<td>0.83</td>
<td>6.68</td>
<td>1.07</td>
</tr>
<tr>
<td>F3</td>
<td>23.29</td>
<td>0.7406</td>
<td>0.79</td>
<td>6.25</td>
<td>1.07</td>
</tr>
<tr>
<td>F4</td>
<td>23.02</td>
<td>0.7515</td>
<td>0.80</td>
<td>6.06</td>
<td>1.06</td>
</tr>
<tr>
<td>F5</td>
<td>24.25</td>
<td>0.7942</td>
<td>0.85</td>
<td>6.56</td>
<td>1.07</td>
</tr>
<tr>
<td>F6</td>
<td>24.05</td>
<td>0.7435</td>
<td>0.85</td>
<td>12.52</td>
<td>1.14</td>
</tr>
<tr>
<td>F7</td>
<td>23.56</td>
<td>0.6845</td>
<td>0.75</td>
<td>8.73</td>
<td>1.09</td>
</tr>
<tr>
<td>F8</td>
<td>24.0</td>
<td>0.7423</td>
<td>0.7880</td>
<td>5.64</td>
<td>1.0598</td>
</tr>
<tr>
<td>F9</td>
<td>24.61</td>
<td>0.7845</td>
<td>0.84</td>
<td>6.61</td>
<td>1.07</td>
</tr>
</tbody>
</table>

Morphological Characteristics of All Batches

Aspect ratio nearer to 1 which shows roundness nearer to 100% shows spherical pellets.

Table 4: Morphological Characteristics of Pellets

<table>
<thead>
<tr>
<th>Batch</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
<th>F8</th>
<th>F9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shape</td>
<td>Sphere</td>
<td>Dumbbell + Ellipsoid</td>
<td>Sphere</td>
<td>Sphere</td>
<td>Oval + Sphere</td>
<td>Sphere</td>
<td>Oval + Sphere</td>
<td>Oval + Sphere</td>
<td>Sphere</td>
</tr>
<tr>
<td>Aspect Ratio</td>
<td>1.05</td>
<td>1.4</td>
<td>1.05</td>
<td>1.76</td>
<td>1.11</td>
<td>1.05</td>
<td>1.75</td>
<td>1.77</td>
<td>1.80</td>
</tr>
</tbody>
</table>
Friability
The friability of the pellets tested was below 0.1%, and thus the pellets have desirable hardness and of good quality with respect to friability. The preliminary aim to produce mechanically strong pellets was thereby achieved.

Drug Content
The drug loaded pellets of Metoprolol Succinate prepared. Drug content of all batches are as shown in Table. All values expressed as mean.

<table>
<thead>
<tr>
<th>Batch</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
<th>F8</th>
<th>F9</th>
</tr>
</thead>
<tbody>
<tr>
<td>(%) Friability</td>
<td>0.13</td>
<td>0.12</td>
<td>0.1</td>
<td>0.15</td>
<td>0.13</td>
<td>0.14</td>
<td>0.16</td>
<td>0.15</td>
<td>0.14</td>
</tr>
<tr>
<td>Drug Content</td>
<td>95.22</td>
<td>102.63</td>
<td>99.85</td>
<td>97.07</td>
<td>98.2</td>
<td>98.21</td>
<td>95.07</td>
<td>98.52</td>
<td>98.29</td>
</tr>
</tbody>
</table>

Scanning Electron Microscopy (SEM)
Surface of pellets as shown in SEM photograph was smooth and sphericity was also good and size of pellets was found to be 960 μm to 1010.21 μm and ratio of length to width (Aspect ratio) is 1.041 which indicate pellets are spherical in shape.

![](image1.png)

Figure 7: SEM analysis of F3 batch

In-Vitro Drug Release Studies
These drug release controlled due to Eudragit L & Ethyl Cellulose as it is hydrophobic. In-vitro drug release study of all formulation batches (F1 to F9) were performed in triplicate using USP apparatus Type-I (Basket).

% Cumulative drug release from batch (F1-F9)

![](image2.png)

Figure 8: In-vitro % Drug release of all Factorial batches
Kinetics of Drug Release

In-Vitro Release Kinetics and Mechanism

The pellets, release data was evaluated by model-dependent (curve fitting) method using PCP Disso-v3 software and model with the higher correlation coefficient was considered to be the best model. To know the release mechanism and kinetics of formulations (F3) were attempted to fit into mathematical models. R² were taken as criteria for selecting the most appropriate model. The Korsmeyer-Peppas kinetic model was best fit for formulation (F3) (R² = 0.9739); represented in Table 6.

![Figure 9: In-vitro Release Kinetics](image)

<table>
<thead>
<tr>
<th>Table 6: Drug Release Kinetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zero order</td>
</tr>
<tr>
<td>0.4032</td>
</tr>
</tbody>
</table>

Best Fit Model

Stability Study

The selected formulations were packed in their final (amber coloured glass) containers and are tightly closed with the cap. They were stored at the stated conditions for three months. Samples were analyzed after 0, 30, 60 and 90 days and they were evaluated.

<table>
<thead>
<tr>
<th>Table 7: Stability studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameters</td>
</tr>
<tr>
<td>Changes in appearances</td>
</tr>
<tr>
<td>Clarity</td>
</tr>
<tr>
<td>Surface texture</td>
</tr>
<tr>
<td>Drug content (%)</td>
</tr>
</tbody>
</table>

CONCLUSION

The objective of the study was to prepare and evaluate metoprolol loaded pellets by extrusion/spheronization for controlled release. It was observed that Eudragit L enhanced the release of metoprolol from drug loaded pellets whereas ethyl cellulose retarded the same. In order to obtain a controlled delivery, a combination of these polymers in different concentration was tried. It was concluded that a combination of Eudragit L and ethyl cellulose in 4% w/v and 6% w/v respectively showed controlled release (98.05 % in 12 hr).
ACKNOWLEDGEMENTS
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REFERENCES

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