Design, Development and Characterization of Metoprolol Succinate Extended Release MUPS Tablets using Various Pelletization Technologies

G. Lakshmi Narayana Reddy1,2, K. Rajnarayana1 and K.N. Jayaveera1
1RA Chem Pharma Ltd, Hyderabad, Telengana, 500 076.
2Department of Chemistry, Vemu Institute of Technology, P. Kothakota, Chittoor (Dist), A.P.

ABSTRACT

Metoprolol is used as an anti hypertensive. Owing to its extensive first pass metabolism, short biological half life and multiple daily dosing, Metoprolol lends itself as an ideal candidate for development of once a day extended release (ER) formulation. Metoprolol succinate ER pellets are prepared by employing various pelletization techniques i.e. powder layering, extrusion & spherodization and wurster process, ethylcellulose as a release modifier and polyethylene glycol as plasticizer. Optimized pellets are compressed into tablets and evaluated for various physico-chemical properties.

Keywords

Metoprolol Succinate,
Extended Release,
Multiparticulates,
Pelletization Techniques.

Introduction

Oral drug delivery has been most commonly used route of administration among all the routes that have been used for the systemic delivery of drugs via various pharmaceutical products of different dosage forms. The objective in designing modified (sustained, controlled or extended) delivery systems is to reduce the dosing frequency and occurrence of toxicity or to increase efficacy of the drug.

Metoprolol is an antihypertensive agent. It has the oral bioavailability of around 50%, which resulted from its extensive first pass metabolism. It has a plasma elimination half-life of around 3 to 4 hours. Owing to its extensive first pass metabolism, short biological half life and multiple daily dosing, Metoprolol succinate lends itself as an ideal candidate for development of once a day extended release (ER) formulation.

Recent trends indicate that multi-particle drug delivery systems are especially suitable for achieving extended release oral formulations with low risk of dose dumping, flexibility of blending to attain different release patterns as well as reproducible and short gastric residence time. The release of drug from pellets depends on a variety of factors including the core type, concentration of release retardant and plasticizer, technique employed for preparation of pellets. Hence, in the present study, an attempt has been made to develop the extended-release MUPS tablets of Metoprolol Succinate employing various pelletization techniques such as powder layering by conventional coating pan, extrusion & spherodization and Wurster process. Ethylcellulose is used as a release retardant. Extended release pellets and MUPS tablets are evaluated for various physical and chemical properties.

Materials

Metoprolol Succinate procured from Polya drugs Laboratories Pvt. Ltd, MCC Spheres procured from M B Sugars & pharmaceuticals, Microcrystalline cellulose (MCC PH 102) and Croscarmelllose sodium are obtained from FMC Biopolymer, Sucrose from E.I.D Parry Limited, Colloidal silicon dioxide from EVONIK Industries, Hypromellose and HPC from Shin Etsu Chemicals, Polyethylene glycol 6000 from Clariant Chemicals, Magnesium Stearate from Polymer Additives Inc, Maize Starch from Roquette, Hydrenated Vegetable Oil (Lubritab), Sodium stearyl fumarate and Silicified Microcrystalline Cellulose from JRS Pharma, Ethylcellulose from Colorcon.

Methods

Preparation of Metoprolol Succinate extended release pellets

Drug loaded pellets of Metoprolol Succinate was prepared by employing three different techniques such as powder layering by conventional coating pan, Extrusion & spherodization and wuster process. These drug loaded pellets were coated with various concentrations of an extended release coating polymer (Ethocel at 7 to 10%w/w) and plasticizer (Polyethylene glycol at 10 to 20%w/w of polymer) using wurster process. Extended release pellets were evaluated for various physico-chemical properties. Extended release pellets were blended with placebo granules and then compressed in to MUPS tablets using 8 station rotary tableting machine, equipped with 9.0 mm round punches. The tablets were subjected for various physico - chemical properties. The optimized tablet formulations of each technique coated with film coating polymer. Composition of the optimized formulation of extended release pellets and tablets presented below.
Determination of Bulk Density and Tapped Density

An accurately weighed quantity of the pellets/lubricated blend (W) was carefully poured into the graduated cylinder and volume (V₀) was measured. Then the graduated cylinder was filled with lid and set into the tap density tester (USP). The density apparatus was set for 500 taps and measured the volume (V₁) after completion of tapping’s. The operation was continued till the two consecutive readings were equal.

The bulk density and the tapped density were calculated using the following formulae.

\[ \text{Bulk density} = \frac{W}{V_0} \]
\[ \text{Tapped density} = \frac{W}{V_1} \]

Where, \( W \) = Weight of the powder/pellets, \( V_0 \) = Initial volume, \( V_1 \) = final volume

Characterization of the Metoprolol Succinate ER pellets & Lubricated Blend

The bulk density and tapped density were calculated using the following formulae.

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\[ \text{Tapped density} = \frac{W}{V_1} \]

Where, \( W \) = Weight of the powder/pellets, \( V_0 \) = Initial volume, \( V_1 \) = final volume

Table 1. Drug loaded pellets prepared by powder layering (Conventional coating pan) followed by ER coating & tablet compression.

<table>
<thead>
<tr>
<th>Composition</th>
<th>% w/w</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug loading</td>
<td></td>
</tr>
<tr>
<td>MCC Spheres (#50 -#60)</td>
<td>17.9</td>
</tr>
<tr>
<td>Metoprolol Succinate</td>
<td>66.0</td>
</tr>
<tr>
<td>Sucrose</td>
<td>3.0</td>
</tr>
<tr>
<td>Colloidal silicone dioxide</td>
<td>1.0</td>
</tr>
<tr>
<td>Hypermellose</td>
<td>3.0</td>
</tr>
<tr>
<td>Purified Water</td>
<td>Q.S</td>
</tr>
<tr>
<td>Extended release coating</td>
<td></td>
</tr>
<tr>
<td>Drug loaded pellets</td>
<td>88.52</td>
</tr>
<tr>
<td>Ethyl cellulose N-50</td>
<td>8.5</td>
</tr>
<tr>
<td>Polyethylene glycol 6000</td>
<td>1.28</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>1.7</td>
</tr>
<tr>
<td>Isopropyl Alcohol</td>
<td>Q.S</td>
</tr>
<tr>
<td>Purified Water</td>
<td>Q.S</td>
</tr>
<tr>
<td>Tablet compression &amp; Coating</td>
<td></td>
</tr>
<tr>
<td>Extended release coated pellets</td>
<td>151.52</td>
</tr>
<tr>
<td>Placebo granules</td>
<td>218.50</td>
</tr>
<tr>
<td>Core Tablet weight</td>
<td>370.00</td>
</tr>
<tr>
<td>Opadry YS-1-7003</td>
<td>7.00</td>
</tr>
<tr>
<td>Purified water</td>
<td>Q.S</td>
</tr>
<tr>
<td>Coated Tablet weight</td>
<td>377.00</td>
</tr>
</tbody>
</table>

Table 2. Drug loaded pellets prepared by Extrusion & spherodization followed by ER coating & tablet compression

<table>
<thead>
<tr>
<th>Composition</th>
<th>% w/w</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug loading</td>
<td></td>
</tr>
<tr>
<td>MCC PH 101</td>
<td>34.92</td>
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<tr>
<td>Metoprolol Succinate</td>
<td>50.0</td>
</tr>
<tr>
<td>Maize Starch</td>
<td>3.0</td>
</tr>
<tr>
<td>Hypermellose</td>
<td>3.0</td>
</tr>
<tr>
<td>Purified Water</td>
<td>Q.S</td>
</tr>
<tr>
<td>Extended release coating</td>
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</tr>
<tr>
<td>Drug loaded pellets</td>
<td>89.65</td>
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<tr>
<td>Ethyl cellulose N-50</td>
<td>10.00</td>
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<tr>
<td>Polyethylene glycol 6000</td>
<td>0.15</td>
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<tr>
<td>Magnesium Stearate</td>
<td>0.20</td>
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<td>Isopropyl Alcohol</td>
<td>Q.S</td>
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<td>Purified Water</td>
<td>Q.S</td>
</tr>
<tr>
<td>Tablet compression &amp; Coating</td>
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<tr>
<td>Extended release coated pellets</td>
<td>200.00</td>
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<tr>
<td>Placebo granules</td>
<td>170.00</td>
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<tr>
<td>Core Tablet weight</td>
<td>370.00</td>
</tr>
<tr>
<td>Opadry YS-1-7003</td>
<td>7.00</td>
</tr>
<tr>
<td>Purified water</td>
<td>Q.S</td>
</tr>
<tr>
<td>Coated Tablet weight</td>
<td>377.00</td>
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</tbody>
</table>

Table 3. Drug loaded pellets prepared by Wurster process followed by ER coating & tablet compression.

<table>
<thead>
<tr>
<th>Composition</th>
<th>% w/w</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug loading</td>
<td></td>
</tr>
<tr>
<td>MCC Spheres</td>
<td>17.9</td>
</tr>
<tr>
<td>Metoprolol Succinate</td>
<td>66.0</td>
</tr>
<tr>
<td>Hypermellose</td>
<td>7.0</td>
</tr>
<tr>
<td>Purified water</td>
<td>Q.S</td>
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<tr>
<td>Extended release coating</td>
<td></td>
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<tr>
<td>Drug loaded pellets</td>
<td>90.88</td>
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<tr>
<td>Ethyl cellulose N-50</td>
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<tr>
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<tr>
<td>Magnesium Stearate</td>
<td>1.5</td>
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<td>Isopropyl Alcohol</td>
<td>Q.S</td>
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<tr>
<td>Purified Water</td>
<td>Q.S</td>
</tr>
<tr>
<td>Tablet compression &amp; Coating</td>
<td></td>
</tr>
<tr>
<td>Extended release coated pellets</td>
<td>151.52</td>
</tr>
<tr>
<td>Placebo granules</td>
<td>218.50</td>
</tr>
<tr>
<td>Core Tablet weight</td>
<td>370.00</td>
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<tr>
<td>Opadry YS-1-7003</td>
<td>7.00</td>
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<tr>
<td>Purified water</td>
<td>Q.S</td>
</tr>
<tr>
<td>Coated Tablet weight</td>
<td>377.00</td>
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</tbody>
</table>

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 was calculated by using the following formulae:

\[ CI = \frac{(TD - BD)}{TD} \times 100 \]

Where, TD is the tapped density and BD is the bulk density.

Hausner’s Ratio

It is the ratio of tapped density and bulk density, which was related to inter particle friction and, as such, could be used to predict powder flow properties. Generally a value less than 1.25 indicates good flow properties, which is equivalent to 20% of Carr’s index.

Angle of Repose

The angle of repose of granules was determined by the funnel-method. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in such a manner that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone measured and angle of repose was calculated using the following equation.

\[ \tan \theta = \frac{h}{r} \]

Where h and r are the height and radius of the powder cone, \( \theta \) is the angle of repose.

Characterization of the Compressed Tablets

Thickness and Hardness

Twenty tablets from the representative sample were randomly taken and individual tablet thickness and hardness were measured by using digital Tablet thickness and Hardness tester. Average thickness and hardness were calculated.

Friability Test

From each batch, ten tablets were accurately weighed and placed in the friability test apparatus (Roche friabilator). Apparatus was operated at 25 rpm for 4 minutes and tablets were observed while rotating. The tablets were then taken after 100 rotations, dedusted and reweighed. % friability was calculated as follows:

\[ \% \text{ Friability} = \frac{(W_1 - W_2)}{W_1} \times 100 \]

Where \( W_1 \) = Initial weight of tablets, \( W_2 \) = Final weight of tablets after testing.

Friability values less than 1.0% are generally acceptable.
Drug content

Preparation of Sample Solution
Weigh and transfer powdered pellets equivalent to 100 mg of Metoprolol Succinate into a 100 mL volumetric flask add 70 mL of methanol, sonicate for 30 minutes and make up to the mark with methanol, filter the solution through 0.45µm nylon membrane filter. Transfer 5.0mL of the resulting solution into a 50mL volumetric flask and make up to the mark with diluent.

Calculate the % assay by using following formula

\[ \frac{R_U \times 5}{W_S \times 100} \times \frac{50}{P} \]

Where,
- \( R_U \) = Peak area of Metoprolol Succinate in sample solution
- \( R_S \) = Average peak area of Metoprolol Succinate in standard solution.
- \( W_S \) = Weight of Metoprolol Succinate working standard taken in mg
- \( W_T \) = Weight of sample taken in mg
- \( P \) = Purity of Metoprolol Succinate working standard used (on as is basis)

% assay

\[ \frac{RU}{RT \times 100} \times 100 = \frac{5}{50} \times \frac{50}{P} \times \frac{100}{100} \]

In vitro drug release studies

Dissolution Parameters
Medium: pH 6.8 phosphate buffer
Apparatus: USP Type II (paddle)
RPM: 50
Volume: 500 mL
Time: 1st, 4th, 8th and 20th hours

Preparation of Sample solution
Set the parameters of dissolution apparatus as mentioned above. Transfer the pellets equivalent to 190mg of Metoprolol Succinate into each individual bowls and operate the dissolution apparatus, withdraw 10 mL of the sample solution through 10µm dissolution filter after 1st, 4th, 8th and 20th hours from each dissolution jars and replace with same volume of dissolution medium previously maintained at 37.0±0.5°C. Filter the solution through 0.45µ Nylon filter.

Calculations
Metoprolol Succinate (% Labeled Amount)

\[ \frac{A_T \times 100}{W_S \times 5 \times 500 \times P} \]

Where,
- \( A_T \) = Area of Metoprolol Succinate in sample solution,
- \( A_S \) = Avg Area of Metoprolol Succinate in standard solution,
- \( W_S \) = Weight of Metoprolol Succinate working standard taken in mg
- \( W_T \) = Weight of the sample taken in mg
- \( P \) = Purity of Metoprolol Succinate working standard used (on as is basis)

Results and Discussion

Characterization of Metoprolol Succinate ER Pellets
Impact of Polymer & plasticizer concentration

Drug loaded pellets prepared by Powder layering (Conventional coating pan)
The drug loaded pellets prepared by powder layering were coated with ER polymer (Ethocel) at various concentrations (7.0, 8.5 and 10.0 %w/w). The impact of the polymer concentration on drug release rate was evaluated.

Figure 1. Impact of polymer concentration on drug release of Metoprolol Succinate ER Pellets (Drug loaded pellets prepared by Powder layering)
From the obtained results, 8.5%w/w of polymer concentration was selected for further studies. These ER Coated pellets were further evaluated to study the impact of plasticizer concentration (10, 15 & 20%w/w of polymer concentration) on drug release rate.

Figure 2. Impact of plasticizer concentration on drug release of Metoprolol Succinate ER Pellets (Drug loaded pellets prepared by Powder layering)
From the obtained results, plasticizer with 15%w/w of polymer concentration was selected as an optimum to get the desired drug release profile. These optimized ER pellets were lubricated with placebo granules and compressed to tablets and evaluated for various physico-chemical properties.

Drug loaded pellets prepared by Extrusion & Spheronization
The drug loaded pellets prepared by extrusion & spheronization were coated with ER polymer (Ethocel) at various concentrations (8.5 and 10.0 %w/w). The impact of the polymer concentration on drug release rate was evaluated.

From the obtained results 10.0 %w/w of polymer concentration was selected for further studies. These ER Coated pellets were further evaluated to study the impact of plasticizer concentration (10, 15 & 20%w/w of polymer concentration) on drug release rate.

From the obtained results, plasticizer concentration of 15%w/w with respect to polymer was selected for further studies. These optimized ER pellets were lubricated with placebo granules and compressed to tablets and evaluated for various physico-chemical properties.
Drug loaded pellets prepared by Wurster process

The drug loaded pellets prepared by wurster process were coated with ER polymer (Ethocel) at various concentrations (8.5, 7.0 and 7.5 %w/w). The impact of the polymer concentration on drug release rate was evaluated.

From the obtained results, polymer concentration of 7.0%w/w was selected for further studies. These ER coated pellets were subjected for evaluation of impact of plasticizer concentration.

Table 4. Physical Properties of Lubricated Blend

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Bulk Density (g/mL)</th>
<th>Tapped Density (g/mL)</th>
<th>Carr’s Index</th>
<th>Hauser’s ratio</th>
<th>Angle repose (θ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>0.703</td>
<td>0.789</td>
<td>10.90</td>
<td>1.122</td>
<td>27.7</td>
</tr>
<tr>
<td>T2</td>
<td>0.716</td>
<td>0.803</td>
<td>10.83</td>
<td>1.122</td>
<td>31.7</td>
</tr>
<tr>
<td>T3</td>
<td>0.722</td>
<td>0.792</td>
<td>8.84</td>
<td>1.097</td>
<td>25.6</td>
</tr>
</tbody>
</table>

Characterization of Metoprolol Succinate ER MUPS tablets

The Metoprolol Succinate extended release tablets were evaluated for various physical properties (Thickness, hardness and friability) and are well within the acceptance criteria. The drug content of all the formulations is within the range of 97.5%-w/w to 102.0%-w/w.

In-vitro drug release studies

According to the above results, the plasticizer concentration 15%/w/w with respect to polymer was selected for further studies. These optimized ER pellets were lubricated with placebo granules and compressed to tablets and evaluated for various physico-chemical properties.

Characterization of Lubricated blend

The lubricated blend of the Metoprolol Succinate ER pellets & placebo granules were characterized with respect to angle of repose, bulk density, tapped density and Carr’s index (Table 4). Angle of repose was less than 32° and Carr’s index values were less than 11 for the granules of all the batches indicating good to fair flowability and compressibility. Hauser’s ratio was less than 1.25 for all the batches indicating good flow properties.

Table 4. Physical Properties of Lubricated Blend

The Metoprolol Succinate extended release tablets were characterized with respect to angle of repose, bulk density, tapped density and Carr’s index (Table 4). Angle of repose was less than 32° and Carr’s index values were less than 11 for the granules of all the batches indicating good to fair flowability and compressibility. Hauser’s ratio was less than 1.25 for all the batches indicating good flow properties.
From the present investigation, it was concluded that there is no significant impact of pelletization technique on drug release profiles of prepared ER MUPS tablets, though there was a difference in polymer concentrations. The drug release of all the formulations followed the first order kinetics and as the n value is less than 0.89; the mechanism of drug release is found to be non fickian diffusion/anomalous behavior.

**Acknowledgment**

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**References**


