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

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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 in to tablets and evaluated for various physic-chemical properties.

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-particulate 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 Polydrugs Laboratories Pvt. Ltd, MCC Spheres procured from M B Sugars & pharmaceuticals, Microcrystalline cellulose (MCC PH 102) and Croscarmellose 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, Hydrgenated 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.

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

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

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

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

Characterization of the Metoprolol Succinate ER pellets & Lubricated Blend [7-8]

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 (V_0) was measured. Then the graduated cylinder was closed with lid and set into the tap density tester (USP). The density apparatus was set for 500 taps and measured the volume (V_f) 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.

Bulk density = W/V_0

Tapped density = W/V_f

Where, W= Weight of the powder/pellets, V_0 = Initial volume, V_f = final volume

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

Composition	%w/w
Drug loading	
MCC Spheres	17.9
Metoprolol Succinate	66.0
Hypromellose	7.0
Purified water	Q.S
Extended release coating	
Drug loaded pellets	90.88
Ethyl cellulose N-50	7.5
Polyethylene glycol 6000	0.125
Magnesium Stearate	1.5
Isopropyl Alcohol	Q.S
Purified Water	Q.S
Tablet compression & Coating	
Extended release coated pellets	151.52
Placebo granules	218.50
Core Tablet weight	370.00
Opadry YS-1-7003	7.00
Purified water	Q.S
Coated Tablet weight	**377.00**

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 = (TD-BD) x 100/TD

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.

$\tan \theta = h/r$

Where h and r are the height and radius of the powder cone, θ 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

% Friability = $(W_1 - W_2) \times 100/W_1$

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

$$= \frac{R_U}{R_S} \times \frac{W_S}{50} \times \frac{5}{50} \times \frac{100}{W_T} \times \frac{50}{5} \times \frac{P}{100} \times 100 = \text{-----}\%$$

% assay

$$\% \text{ of label amount} = \frac{\text{-----}}{\text{Label claim in mg}} \times 100$$

Where,

Ru = Peak area of Metoprolol Succinate in sample solution

Rs = Average peak area of Metoprolol Succinate in standard solution.

Ws =Weight of Metoprolol Succinate working standard taken in mg

WT = Weight of sample taken in mg

P = Purity of Metoprolol Succinate working standard used (on as is basis)

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 1^{st}, 4^{th} , 8^{th} and 20^{th} 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)

$$\frac{A_T}{A_S} \times \frac{W_S}{50} \times \frac{5}{50} \times \frac{500}{W_T} \times \frac{P}{\text{Label claim in \%}} \times 100 = \text{----}\%$$

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.

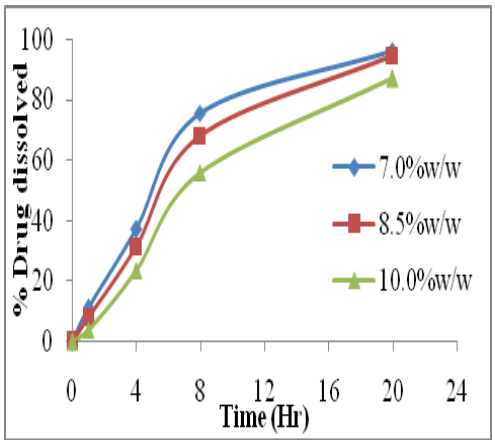

Figure 1. Impact of polymer concentration on drug release of Metoprolol Succinate ER Pellets (Drug loaded pellets prepared by Powder layering)

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.

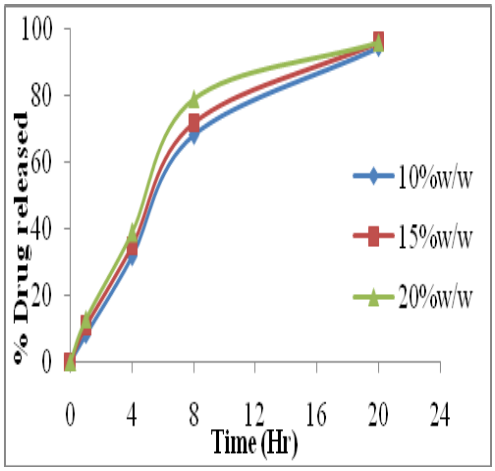

Figure 2. Impact of plasticizer concentration on drug release of Metoprolol Succinate ER Pellets (Drug loaded pellets prepared by Powder layering)

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 & Spherodization

The drug loaded pellets prepared by extrusion & spherodization 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.

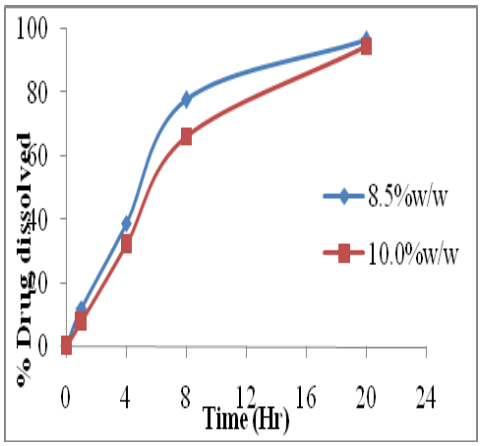

Figure 3. Impact of polymer concentration on drug release of Metoprolol Succinate ER Pellets (Drug loaded pellets prepared by extrusion spherodization)

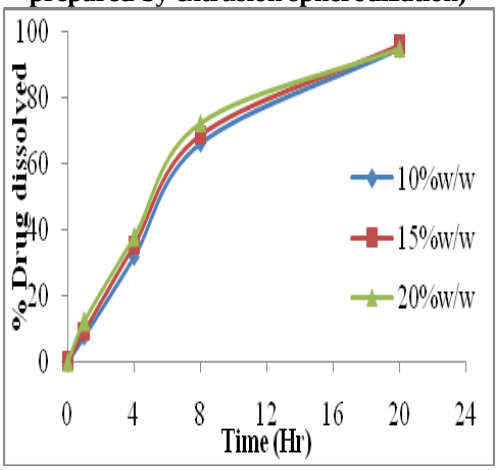

Figure 4. Impact of plasticizer concentration on drug release of Metoprolol Succinate ER Pellets (Drug loaded pellets prepared by extrusion spherodization)

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.

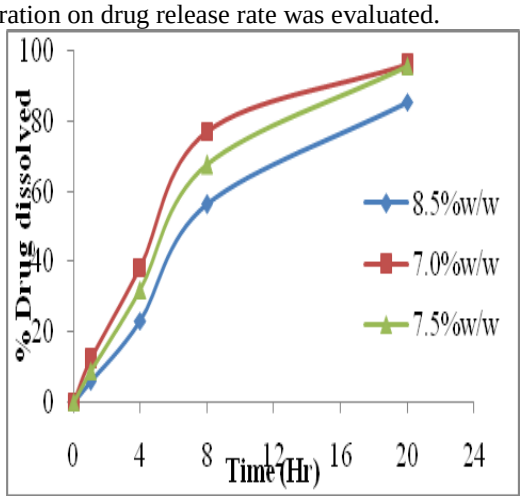

Figure 5. Impact of polymer concentration on drug release of Metoprolol Succinate ER Pellets (Drug loaded pellets prepared by wurster process)

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.

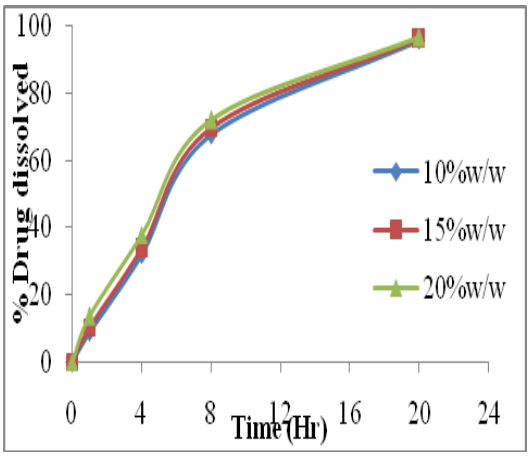

Figure 6. Impact of plasticizer concentration on drug release of Metoprolol Succinate ER Pellets (Drug loaded pellets prepared by wurster process)

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. Hausner's ratio was less than 1.25 for all the batches indicating good flow properties.

Table 4. Physical Properties of Lubricated Blend

Formulation	Bulk Density (g/mL)	Tapped Density (g/mL)	Carr's Index	Hausner's ratio	Angle repose (θ)
T1	0.703	0.789	10.90	1.122	27.7
T2	0.716	0.803	10.83	1.122	31.7
T3	0.722	0.792	8.84	1.097	25.6

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

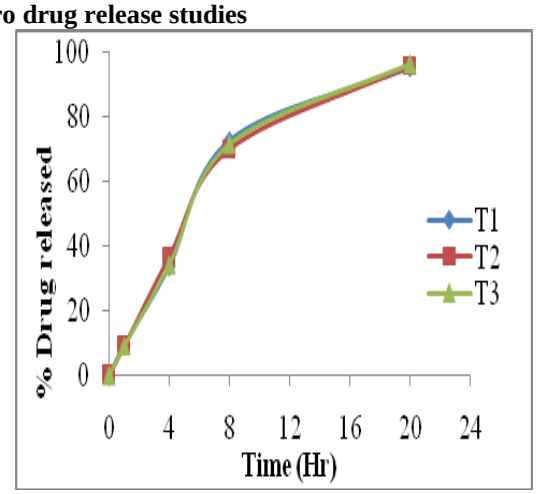

Figure 7. Comparative dissolution profiles of Metoprolol Succinate extended release tablets in pH 6.8 Phosphate buffer

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.

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