

Development and *In Vitro-In Vivo* Evaluation of Extended-release Multiple-unit Pellet System Tablets of Metoprolol Succinate

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Abstract

Aim: To design, develop, and evaluate the metoprolol succinate extended-release (ER) multiple-unit pellet system (MUPS) tablets. **Materials and Methods:** Metoprolol succinate ER pellets were prepared using Wurster process. The impact of the various concentrations of polymer and plasticizers were studied. Further optimized metoprolol succinate ER pellets were compressed into MUPS tablets and evaluated for various physico-chemical and pharmacokinetic parameters. **Results and Discussion:** Metoprolol succinate ER MUPS tablets prepared by using 7.5% w/w of ethocel as release retardant and 15% w/w of the plasticizer with respect to the polymer. The release extended for 20 h. **Conclusion:** Research work indicates that the test formulation was able to extend the delivery of metoprolol in the desired rate.

Key words: Extended-release, metoprolol succinate, multiparticulates, multiple-unit pellet system tablets

INTRODUCTION

Metoprolol is a β_1 selective adrenoceptor antagonist used in the treatment of angina and hypertension. Peak plasma concentration occurs about 1.5 h after a single oral dose. The half-life of metoprolol is about 3-4 h. It is readily and completely absorbed from the gastrointestinal tract. However, it is subjected to considerable first pass metabolism. The main objective of the present study is to develop and evaluate extended-release (ER) multiple-unit pellet system (MUPS) tablets of metoprolol succinate using Wurster process followed by compression.^[1,2]

Polymer Additives Inc.; hydrogenated vegetable oil (Lubritab), sodium stearyl fumarate, and silicified microcrystalline cellulose from JRS Pharma; ethyl cellulose from Colorcon. All other reagents used were a high-performance liquid chromatography (HPLC) grade or analytical grade received from Qualigens Fine Chemicals and Merck (India).

Methods

Design and development of metoprolol succinate ER MUPS tablets

Drug loaded pellets of metoprolol succinate were prepared by coating the drug suspension onto the inert core (MCC Spheres) employing Wurster process. Drug loaded pellets were further coated with the ER coating polymer (Ethocel N 50) at various concentrations (8.5%, 7.0%, and 7.5% w/w) to study the impact of polymer concentration on drug release. Further,

MATERIALS AND METHODS

Materials

Metoprolol succinate procured from Polydrugs Laboratories Pvt. Ltd.; MCC spheres procured from M B Sugars & Pharmaceuticals; hypromellose and HPC from Shin-Etsu Chemicals; polyethylene glycol 6000 from Clariant Chemicals; magnesium stearate from

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different concentrations (10%, 15%, and 20% w/w with respect to polymer) of plasticizer were evaluated to study the impact on drug release. Optimized pellets were blended with lubricated placebo granules and compressed into tablets using rotary tablet compression machine, equipped with 9.0mm punches. Further, these compressed tablets were coated with film coating polymer. Film-coated tablets were evaluated for various physico-chemical properties and *in-vivo* studies. The composition of the optimized formulation represented in Table 1.

Characterization of the metoprolol succinate ER pellets and tablets^[3]

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 h

Preparation of sample solution

Set the parameters of dissolution apparatus as mentioned above transfer the metoprolol succinate ER pellets/MUPS tablets into each individual bowls and operate the dissolution

apparatus, withdraw 10 ml of the sample solution through 10 µm dissolution filter after 1st, 4th, 8th, and 20th h from each dissolution jars and replace with same volume of dissolution medium previously maintained at 37.0 ± 0.5°C. Filter the solution through 0.45 µ 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 = Average 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).

Thickness and hardness

About 20 tablets from the representative sample were randomly taken, and individual tablet thickness and hardness were measured using digital tablet thickness and hardness tester. Average thickness and hardness were calculated.

Friability test

From each batch, 10 tablets were accurately weighed and placed in the friability test apparatus (Roche friabilator). Apparatus was operated at 25 rpm for 4 min, and tablets were observed while rotating. The tablets were then taken after 100 rotations, dedusted and reweighed.

% Friability was calculated as follows:

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

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

Friability values <1.0% are generally acceptable.

Drug content

Preparation of sample solution

Weigh and transfer powdered pellets/tablets equivalent to 100 mg of metoprolol succinate into a 100 ml volumetric flask add 70 ml of methanol sonicate for 30 min and makeup to the mark with methanol, filter the solution through 0.45 µm nylon membrane filter. Transfer 5.0 ml of the resulting solution into a 50 ml volumetric flask and makeup to the mark with diluent.

Calculate the % assay using following formula:

$$\frac{R_u}{R_s} \times \frac{W_s}{50} \times \frac{5}{50} \times \frac{100}{W_T} \times \frac{50}{5} \times \frac{P}{100} \times 100 = \text{\%}$$

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

Table 1: Composition of the optimized formulation of metoprolol succinate ER MUPS tablets

Composition	%w/w
Metoprolol succinate ER pellets	
Drug loading	
MCC spheres	17.9
Metoprolol succinate	66.0
Hypromellose	7.0
Purified water	Q.S
ER 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
Metoprolol succinate ER MUPS tablets	mg/tablet
ER 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

MUPS: Multiple-unit pellet system, ER: Extended release

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).

***In vivo study*^[3]**

Experimental design

The parallel design was selected in which out of six albino male rabbits, three were treated with test formulation (metoprolol succinate ER MUPS tablets) and another one with reference (metoprolol succinate active pharmaceutical ingredient [API]).

Drug administration sample collection

The Institutional Animal Ethics Committee (1722/RO/ERe/S/13/CPCSEA) approved the protocol of the study. Healthy male albino rabbits weighing between 2.0 and 2.5 KG were used. Rabbits were separated into two groups, each consisting of three animals. Reference (metoprolol succinate API) and test formulation (metoprolol succinate ER MUPS tablets) were given orally via silicone rubber gastric intubation tube to the first group and second group, respectively. All the rabbits were housed in individual cages at room temperature, fasted before the 12 h of drug administration and have access to water and food after 4 h of dosing throughout the study period.

Approximately 2 ml of blood sample was collected at proposed time points such as pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 18, and 24 h through a marginal ear vein. All the blood samples were collected into K_2 ethylenediaminetetraacetic acid coated tubes. Samples were centrifuged at 4000 rpm for 5 min. The plasma was separated and stored at -70°C until analysis.

Sample preparation

A simple protein precipitation method was used for the extraction of metoprolol succinate from the rabbit plasma samples. To an aliquot of 100 μl plasma, 300 μl ACN was added. Invert and mix for 15 s on a cyclomixer and vortex for 2 min; samples were centrifuged at 3000 rpm for 5 min. The supernatant layer was separated and subject to evaporation under liquid nitrogen. Finally, dried samples were reconstituted in the 100 μl of mobile phase and then estimated the content of metoprolol succinate using HPLC method.

Determination of metoprolol from plasma

The HPLC method was used for the estimation of metoprolol from rabbit plasma and pinacidil monohydrate used as an internal standard. The 0.01 M potassium dihydrogen phosphate, acetonitrile, and methanol (55:22.5:22.5) as an eluent. The eluent was detected at 274 nm.

Pharmacokinetic analysis

The pharmacokinetic study was carried out to determine the various parameters such as time to reach maximum concentration (T_{\max}), maximum plasma concentration (C_{\max}), the area under the curve ($AUC_{0-\text{inf}}$). The values of T_{\max} and C_{\max} were noted from the arrhythmic plot of time versus plasma concentration of metoprolol. The AUC was determined by trapezoidal rule.

RESULTS AND DISCUSSION

In vitro drug release studies of pellets

The drug loaded pellets 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 1].

From the obtained results, polymer concentration of 7.5%w/w was selected for further studies. These ER coated pellets were subjected for evaluation of the impact of plasticizer concentration [Figure 2].

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.

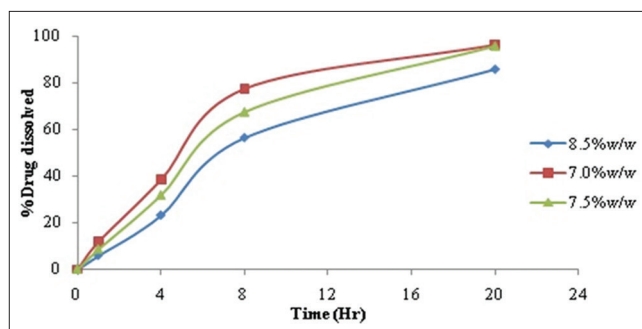


Figure 1: Impact of polymer concentration on drug release of metoprolol succinate extended-release pellets

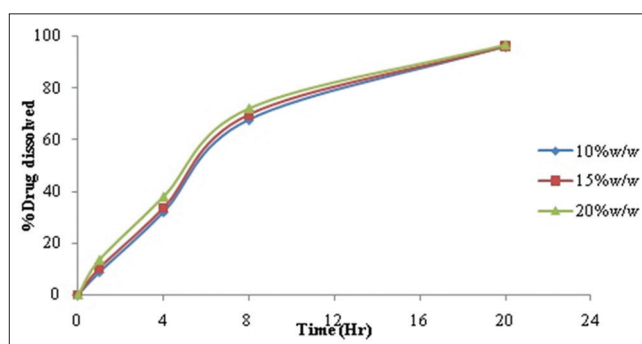


Figure 2: Impact of plasticizer concentration on drug release of metoprolol succinate extended-release pellets

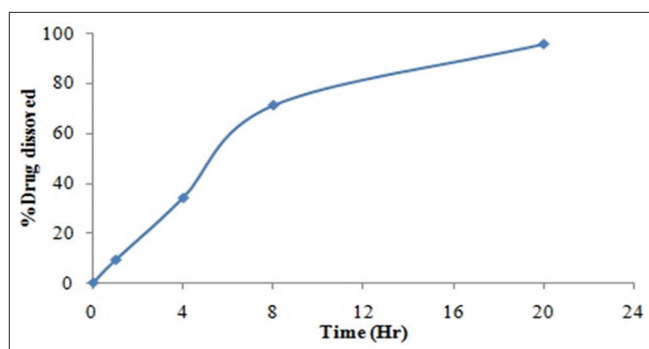


Figure 3: *In vitro* drug release profile of metoprolol succinate extended-release tablets

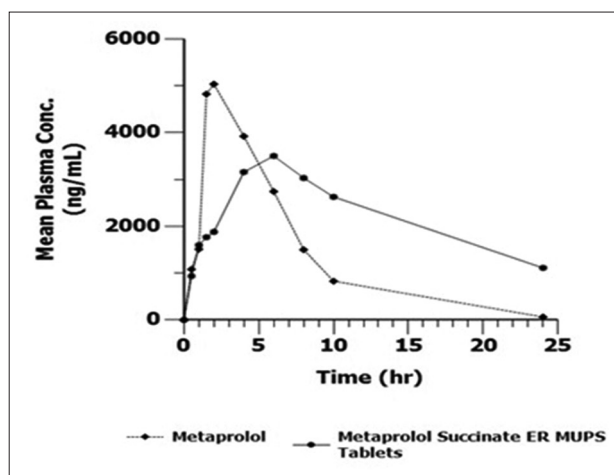


Figure 4: Plasma concentration-time profile of metoprolol and metoprolol succinate extended-release multiple-unit pellet system tablets

Characterization of tablets

The metoprolol succinate ER tablets were evaluated for various physical properties (thickness, hardness, and friability) and were well within the acceptance criteria. The drug content of all the formulations is within the range of 97.5-102.0% w/w [Figure 3].

The drug release followed the first order kinetics and as the n value is <0.89 ; the mechanism of drug release is found to be non-fickian diffusion/anomalous behavior.

In vivo studies

The pharmacokinetic parameters of the metoprolol succinate ER MUPS tablets were described in Figure 4 and Table 2.

CONCLUSION

From the present investigation, it was concluded that the metoprolol succinate ER MUPS tablets were successfully developed. The pharmacokinetic evaluation of the metoprolol

Table 2: Summary of pharmacokinetic parameters for test and reference

Pharmacokinetic parameters	Reference (metoprolol succinate)	Test formulation (metoprolol succinate ER MUPS tablets)
C_{max} (ng/mL)	5240±9.2	3500±9.2
T_{max} (h)	1.83±0.2	6.00±0.3
AUC_{0-t} (h*ng/mL)	30,900±249.5	51,100±265.7
$AUC_{0-\infty}$ (h*ng/mL)	31,200±252.3	69,200±261.2
$T_{1/2}$ (h)	3.65±0.3	11.2±0.1

AUC: Area under the curve, MUPS: Multiple-unit pellet system, ER: Extended release

succinate ER MUPS tablets against metoprolol succinate API in rabbits, results in the sustained T_{max} and prolonged $t_{1/2}$ indicate an ER of metoprolol from ER MUPS Tablets in comparison with metoprolol succinate (API). The results indicate that test formulation was able to extend the delivery of metoprolol in the desired rate.

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