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**RESEARCH ARTICLE**

# Modulation of drug (metoprolol succinate) release by inclusion of hydrophobic polymer in hydrophilic matrix

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**Abstract**

The objective of this study was to develop sustained release (SR) matrix tablets of metoprolol succinate (MS), by using different polymer combinations and fillers, to optimize by response surface methodology and to evaluate biopharmaceutical parameters of the optimized product. Matrix tablets of various combinations were prepared with cellulose-based polymers: hydroxy propyl methyl cellulose (HPMC) and ethyl cellulose (EC); and lactose and dibasic calcium phosphate dihydrate (DCP) as fillers. Study of pre-compression and post-compression parameters facilitated the screening of a formulation with best characteristics that underwent here optimization study by response surface methodology (Central Composite Design). The optimized tablet was subjected to further study like scanning electron microscopy, swelling study and *in vivo* study in rabbit model. Both *in vitro* and *in vivo* study revealed that combining of HPMC K100M (21.95%) with EC (8.85%), and use of DCP as filler sustained the action up to 12 h. The *in vivo* study of new SR tablets showed significant improvement in the oral bioavailability of MS in rabbits after a single oral dose of 25 mg. The delayed $T_{max}$ and lower $C_{max}$ indicated a slow and SR of MS from the optimized matrix tablets in comparison with the immediate release dosage form. The developed SR (MS) tablet of improved efficacy can perform therapeutically better than conventional tablet.

**Keywords:** Metoprolol succinate, HPMC, ethyl cellulose, response surface methodology, IVIVC

## Introduction

The pharmacological and therapeutic benefits of controlled release dosage forms of compounds with short half-lives had been demonstrated repeatedly in the pharmaceutical literature[1]. Sustained release (SR) dosage forms offer many advantages including desired release kinetics, improved drug therapy and patient compliance. Such delivery systems gained wide acceptance owing to their 'simplest monolithic robust forms,[2,3] low cost of product, broad FDA acceptance, easy manufacturing process and favorable *in vivo* performance[4,5].

Hydroxy propyl methyl cellulose (HPMC) is used extensively for 'Hydrophilic Extended Release' matrix tablets owing to its compatible physicochemical properties[6]. Matrix tablets exhibit release phenomenon of complex type because of series of actions such as water penetration, polymer swelling, relaxation of the macromolecular polymeric chains[7], drug dissolution, drug diffusion and matrix erosion. The gel layer formation and its stability are controlled by the concentration, viscosity and chemical structure of the polymer[8]. In short, the mechanism and kinetics of drug release are dependent on the solubility of the active moiety, and the swelling and erosion properties of the polymer[9–11]. Generally, the release of water-soluble moieties will typically follow first order release kinetics. Sole use of hydrophilic matrix material is limited to water-soluble drug owing to its rapid diffusion[12]. The combination of hydrophilic polymer, HPMC and a hydrophobic polymer such as ethyl cellulose (EC) offers a flexible system to tailor the drug release of soluble drugs by selecting suitably substituted variety of polymers[13–15]. EC is non-toxic, stable at varying pH, compressible and inert[16–20]. In general, designing of controlled release drug delivery systems for providing 12 or 24 h zero order release kinetics, especially for water-soluble agents, is often difficult owing

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to high burst effect, uncontrolled polymer relaxation and disentanglement, shorter path of diffusion[21]. Metoprolol Succinate (MS), a soluble drug is chosen as model drug to develop its SR dosage form. It is a $\beta_1$-Adrenergic receptor blocking agent and is used in the management of cardiovascular diseases. Its elimination half-life is 4–6 h, and it requires dosing every 6 h[22].

The present work aims at (1) fabrication of a simple, elegant and cost effective SR product of MS, (2) understanding the mechanism of drug release from matrix systems with hydrophilic and hydrophobic (HPMC and EC) polymers and fillers (lactose and dicalcium phosphate), (3) optimization of formulation by response surface methodology, (4) evaluation of the oral bioavailability of the optimized formulation by *in vivo* evaluation and its comparison with that of SR matrix tablet, marketed SR tablet and equivalent pure drug, and (5) correlation between *in vitro* drug release and *in vivo* absorption of optimized SR tablet of MS.

## Materials and methods

### Materials

MS was gifted samples from Torrent Laboratories, India. Other excipients acetonitrile (HPLC grade) and methanol (HPLC grade) were purchased from M/s. Qualigens Fine Chemicals, Mumbai, India. Other materials used in the study such as hydroxyl propyl methylcellulose (HPMC K 100M), HPMC E 5, EC (7 cp viscosity grade) were of Pharmacopoeia standard (USP/NF). MS extended-release tablet USP 25 mg (EMBETA XR-25 tab, Batch No. DJ1383, Expiry date: May 2011) was purchased from INTAS Pharmaceuticals, Ahmedabad, India.

### Tablet formulation

Drug, filler and polymer powders were sieved through 80 mesh screen. Drug and filler premixes were mixed thoroughly in a double cone blender (Jyoti Scientific Industries, India, Model No. 1240) with various proportions of HPMC K100M and EC polymers, and then mixed powder was granulated with Methocel E5 (5% w/w) solution in purified water (50°C). The wet mass was passed through 12 mesh screen and dried at 60°C for 30–45 min. Drying was stopped when the loss on drying (LOD) values of post drying samples were within ±1.5% to the preblended samples. The dried granules, after passing through 18 mesh screen, were blended with lubricant/glidant mixture (2% magnesium stearate and 1% Aerosil) and subsequently compressed into tablets on a rotary tablet machine (CIP Machineries Pvt. Ltd., Ahmedabad, India) by the use of round, standard concave tools that target to produce tablet of 100 mg weight and tablet hardness was fixed within the range of 6–8 kg/sq cm. Ten different formulations ($A_i$–$J_i$) were prepared with different proportions of polymers and diluents as per compositions given in Table 1.

### Determination of pre-compression and post-compression parameters

Tap density of granules was determined by a 'tapped density tester' (Electrolab, India). Bulk density of granules, particle size distribution, percent compressibility (Carr's index), Hausner's ratio, angle of repose and rate of granules' flow were determined by USP <1174> method. 'Frequency of size distribution' and 'percent of fines' in the dried granules were determined by sieve analysis. The tablets were stored for at least 6 days at room temperature before characterization. Ten samples were chosen randomly for conducting each test. Micrometer gauge (Mitutoyo, Japan) was used to measure the thickness and diameter of the tablets. Roche friabilator (Camp-bell Electronics, Mumbai) was used to conduct 'Friability test' on coated tablets. Data were tabulated in Tables 2 and 3.

### Study of *in vitro* drug release

The *in vitro* dissolution studies were performed in USP30-type I dissolution apparatus operating at 50 rpm. The dissolution medium consisted of 0.1 N hydrochloric acid for the first 2 h (pH 1.2) and the phosphate buffer at pH 6.8 for the next 3–12 h and the medium (900 mL) was maintained at 37°C ± 0.5°C. An aliquot (5 mL) was withdrawn at specific time intervals and replaced with the same volume of fresh medium at the same temperature. The withdrawn sample was filtered through 0.45 µm filter paper. Its drug content was determined by UV-Visible spectrophotometer (Shimadzu, Kyoto, Japan) at wave length of 280 nm. It was ascertained that none of the ingredients used in the matrix formulations interfered with the assay. The release studies were conducted in triplicate. Cumulative

Table 1. Composition (%) of SR matrix tablets of metoprolol succinate.

| Formulation Code Composition | $A_i$* | $B_i$ | $C_i$ | $D_i$ | $E_i$ | $F_i$ | $G_i$ | $H_i$ | $I_i$ | $J_i$ |
|---|---|---|---|---|---|---|---|---|---|---|
| Metoprolol succinate | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 |
| HPMCK100M | 30 | 25 | 20 | 15 | 10 | 30 | 25 | 20 | 15 | 10 |
| Ethyl cellulose | 0 | 05 | 10 | 15 | 20 | 0 | 05 | 10 | 15 | 20 |
| DCP | 0 | 0 | 0 | 0 | 0 | 37 | 37 | 37 | 37 | 37 |
| Spray dried lactose | 37 | 37 | 37 | 37 | 37 | 0 | 0 | 0 | 0 | 0 |
| HPMC E5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Magnesium stearate | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| Aerosil | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |

*i indicates initial formulation.

drug release (%) was plotted against time of release for all initial formulations ($A_i$–$E_i$; $F_i$–$J_i$) (see Figures 1 and 2).

To further characterize the drug release process, the mean dissolution time (MDT) was calculated according to the following equation:

$$MDT = \frac{\sum_{i=1}^{n} t_{mid} * \Delta Q}{\sum_{i=1}^{n} \Delta Q}$$

where $i$ is the sample number, $n$ is the number of time intervals considered, $t_{mid}$ is the time at midpoint between $t_i$ and $t_i$–1 and $\Delta Q$ the additional amount of drug dissolved in the period of time $t_i$ and $t_i$–1. Data had been tabulated in Table 2.

## RSM optimization– 'Central Composite Design'

The formulation $H_i$ was found to be most desirable from its physical parameters and dissolution study. So it was chosen for optimization. Its polymer compositions were used as the center value. The optimization of SR matrix tablets of MS was done by using design expert software (design expert trial version 7.0.3 State Inc., Minneapolis, MN). A Central Composite Design (CCD) with $\infty = 1$ was employed as per the standard protocol[23,24]. The quadratic response surface methodology is based on the multiple linear regression analysis taking into account the main, the quadratic and the interaction effects according to following equation.

$$Y(\text{response}) = b_0 + \sum_{i=1}^{i=2} b_i X_i + \sum_{i=1}^{i=2} b_{ii} X_{ii}^{\ 2} + \sum_{i<J=2}^{i=2} b_{ij} X_i X_j + e$$

Since two parameters were varied, six β-coefficients (regression coefficients) were to be estimated. Based on the initial studies, polymers HPMC K100M (A) and EC (B) were selected as the independent factors with three levels each. The center point (0, 0) was studied in quintuplicate. All other formulation and processing variables were kept invariant throughout the study. Table 4 summarizes an account of the 13 runs of experimental design, factor combinations (HPMC K100M, EC). Drug release (%) in 8 h ($Rel_{8h}$) was the response variable. Experiments were performed as per Table 4. Data obtained from experimental design were analyzed by the same software which generated response surfaces (Figure 3), analysis of variance (ANOVA) (Table 5). After analyzing ANOVA and deleting insignificant factors, a correlation was obtained. To validate this equation experiments were performed as per check point formulations, CPF1-CPF8 (see Table 6).

Table 2. Characterization of granules ($A_i$–$J_i$) of metoprolol succinate.

| Granules (batch) | Size distribution % wt retained on sieves 20 | 30 | 40 | 60 | % fines | Bulk density (g/mL) | Hausner ratio | Carr's index | Angle of repose (°) | Mass flow rate (g/s) |
|---|---|---|---|---|---|---|---|---|---|---|
| $A_i$ | 78.1 | 9.8 | 6.9 | 3.0 | 2.2 | 0.57 | 1.041 | 17.4 ± 0.6 | 29 ± 0.8 | 8.12 |
| $B_i$ | 76.8 | 11.6 | 6.7 | 2.8 | 2.1 | 0.43 | 1.023 | 21.2 ± 0.3 | 28 ± 0.6 | 8.14 |
| $C_i$ | 79.6 | 10.7 | 3.9 | 3.2 | 2.6 | 0.45 | 1.048 | 20.4 ± 0.4 | 28 ± 0.5 | 8.32 |
| $D_i$ | 80.2 | 11.9 | 3.1 | 2.5 | 2.3 | 0.62 | 1.062 | 19.8 ± 0.6 | 27 ± 0.7 | 8.77 |
| $E_i$ | 81.7 | 9.7 | 3.6 | 2.9 | 2.1 | 0.57 | 1.071 | 19.2 ± 0.4 | 27 ± 0.8 | 8.67 |
| $F_i$ | 81.4 | 10.6 | 3.1 | 2.9 | 2.0 | 0.47 | 1.020 | 16.4 ± 0.9 | 27 ± 0.8 | 7.13 |
| $G_i$ | 80.6 | 10.4 | 3.6 | 2.9 | 2.5 | 0.37 | 1.036 | 21.6 ± 0.6 | 29 ± 1.1 | 7.75 |
| $H_i$ | 78.3 | 11.1 | 3.7 | 3.5 | 3.4 | 0.39 | 1.048 | 17.6 ± 0.7 | 26 ± 0.6 | 7.81 |
| $I_i$ | 79.5 | 11.8 | 3.8 | 3.2 | 1.7 | 0.53 | 1.052 | 19.3 ± 0.9 | 27 ± 0.9 | 7.63 |
| $J_i$ | 78.1 | 10.9 | 5.9 | 2.7 | 2.4 | 0.52 | 1.077 | 19.1 ± 0.8 | 28 ± 0.8 | 7.11 |

Table 3. Characterization of SR matrix tablets of metoprolol succinate.

| Tablet formulations (Batch) | Weight (mg) | Thickness (mm) | Friability (%) | Crushing strength(kg·f) | Drug content (%) | MDT*(h) |
|---|---|---|---|---|---|---|
| $A_i$ | 101.4 ± 2.0 | 2.74 ± 0.01 | 0.58 | 3.78 ± 0.18 | 101.78 ± 0.39 | 3.41 |
| $B_i$ | 102.2 ± 0.8 | 2.85 ± 0.01 | 0.69 | 4.28 ± 0.17 | 102.45 ± 0.62 | 4.15 |
| $C_i$ | 100.7 ± 0.5 | 2.49 ± 0.01 | 0.40 | 5.21 ± 0.14 | 100.32 ± 0.48 | 4.87 |
| $D_i$ | 101.2 ± 0.8 | 2.72 ± 0.01 | 0.62 | 4.23 ± 0.18 | 99.45 ± 0.86 | 4.62 |
| $E_i$ | 100.4 ± 0.7 | 2.61 ± 0.02 | 0.42 | 3.43 ± 0.16 | 103.35 ± 0.56 | 1.57. |
| $F_i$ | 102.6 ± 0.9 | 2.52 ± 0.01 | 0.45 | 5.17 ± 0.17 | 101.65 ± 0.54 | 5.93 |
| $G_i$ | 101.4 ± 0.9 | 2.50 ± 0.01 | 0.37 | 5.34 ± 0.19 | 100.45 ± 0.32 | 4.35 |
| $H_i$ | 100.8 ± 0.5 | 2.54 ± 0.01 | 0.36 | 5.13 ± 0.15 | 101.25 ± 0.26 | 7.59 |
| $I_i$ | 102.6 ± 0.8 | 2.49 ± 0.01 | 0.47 | 6.34 ± 0.11 | 98.78 ± 0.27 | 6.37 |
| $J_i$ | 102.5 ± 0.7 | 2.51 ± 0.01 | 0.54 | 3.82 ± 0.12 | 99.31 ± 0.77 | 2.41 |

*MDT indicates mean dissolution time.
All values represent mean ± SD ($n = 6$)

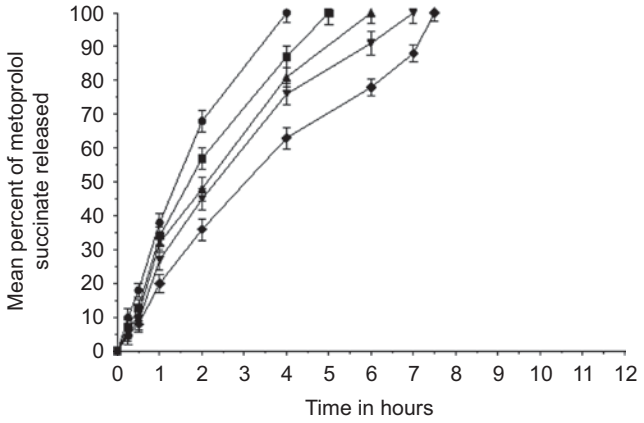


Figure 1. Profiles show the effects of composition of matrix forming polymers (HPMC K100M, EC) and spray dried lactose as filler on the *in vitro* release of metoprolol succinate. Data are represented as mean ± SD ($n=6$). (■)$A_i$ (▲) $B_i$ (◆) $C_i$ (▼) $D_i$ (•) $E_i$.

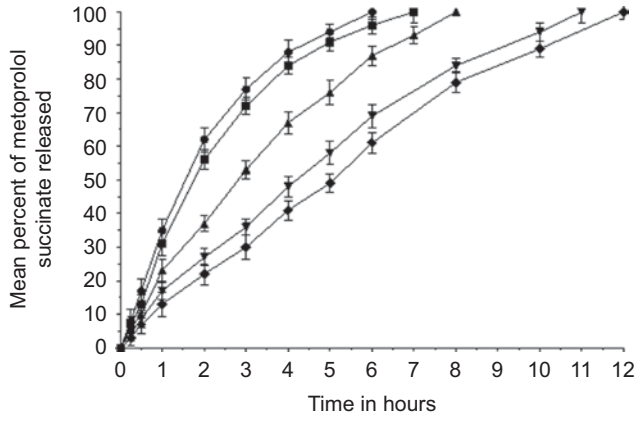


Figure 2. Profiles show the effects of composition of matrix forming polymers (HPMC K100M, EC) and DCP as filler on the *in vitro* release of metoprolol succinate. Data were represented as mean ± SD ($n=6$). (▲)$G_i$ (■) $F_i$ (◆) $H_i$ (▼) $I_i$ (•) $J_i$.

Experimental response data were compared with that of predicted response data (see Table 6). Other statistics such as $R^2$, pure error and lack-of-fit were displayed in Table 5. Following is the developed correlation:

$$R^3 = 90.21 - 1.77A + 5.48A^2 + 1.98B^2$$

Table 7 shows the composition of optimized formulation, CPF8.

## Kinetics and mechanism of drug release

In order to propose a possible drug release mechanism, release data obtained from tablet (CPF8) was fitted to different equations such as zero order ($M=kt$), first order equation ($\ln M=kt$), Higuchi model ($M=k\sqrt{t}$) and Korsemeyer–Peppas equation ($M=kt^n$). $M$ is the amount of drug (%) released after time $t$. $k$ is the release rate constant and $n$ is the exponent. A value of $n=0.5$ indicates case I (Fickian) diffusion, $0.5 < n < 1$ anomalous (non Fickian) diffusion, $n=1$ is for Case II transport and $n>1$ supercase II transport. The entire curve-fitting analysis was performed by GraphPad Prism version 3.02 (GraphPad Software, Inc) and Excel (Microsoft) software. Results (correlation coefficient, $R^2$) were tabulated in Table 8.

Table 4. Experimental design of polymer compositions (factors, *A* and *B*) in tablet formulation.

| | Coded factor | |
|---|---|---|
| Trial no. | *A* | *B* |
| I | −1 | −1 |
| II | −1 | 0 |
| III | −1 | 1 |
| IV | 0 | −1 |
| V | 0 | 0 |
| VI | 0 | 1 |
| VII | 1 | −1 |
| VIII | 1 | 0 |
| IX | 1 | 1 |
| X | 0 | 0 |
| XI | 0 | 0 |
| XII | 0 | 0 |
| XIII | 0 | 0 |

Translation of coded levels in actual units
Coded level: −1 0 1
A, HPMC (mg) 15 20 25
B, EC (mg) 5 10 15

## Determination of swelling and eroding behavior

Matrix tablet (CPF8) was introduced into the dissolution apparatus under the standard conditions of '*in vitro* drug release' study[25]. The tablets were removed and weight of each swollen tablet was determined. To determine erosion, swollen-tablets were placed in a vacuum oven at 40°C for 48 h and then weighed. Swelling (%) and erosion (%) were calculated according to the following formula: where $T$, $S$ and $R$ are the average weights of tablets before swelling (initial), after swelling and after drying (eroded), respectively.

$$\%\ \text{swelling} = S/R \times 100, \text{ and } \%\ \text{erosion} = (T-R)/T \times 100$$

The results are displayed in Figure 4.

## Surface topography by scanning electron microscopy

Matrix tablets (CPF8) were removed from the dissolution apparatus at predetermined time intervals, and the samples for scanning electron microscopy (SEM) were prepared by positioning the matrix tablets on a double-sided adhesive tape stuck to a brass stub. The stubs were then coated with gold to a thickness of ~180–200 Å under a nitrogen atmosphere using a gold sputter module in a high vacuum ($10^{-2}$–$10^{-3}$ Torr) evaporator. Samples were coated with gold and visualized under scanning electron microscope (Jeol JSM-5200, Tokyo, Japan). Photomicrographs of coated samples were shown in Figure 5.

## Effect of storage on the stability of SR matrix tablets of MS

Stability studies were conducted on SR matrix tablets of the optimized batch (CPF8) to assess their chemical stability and therapeutic efficacy by examining their

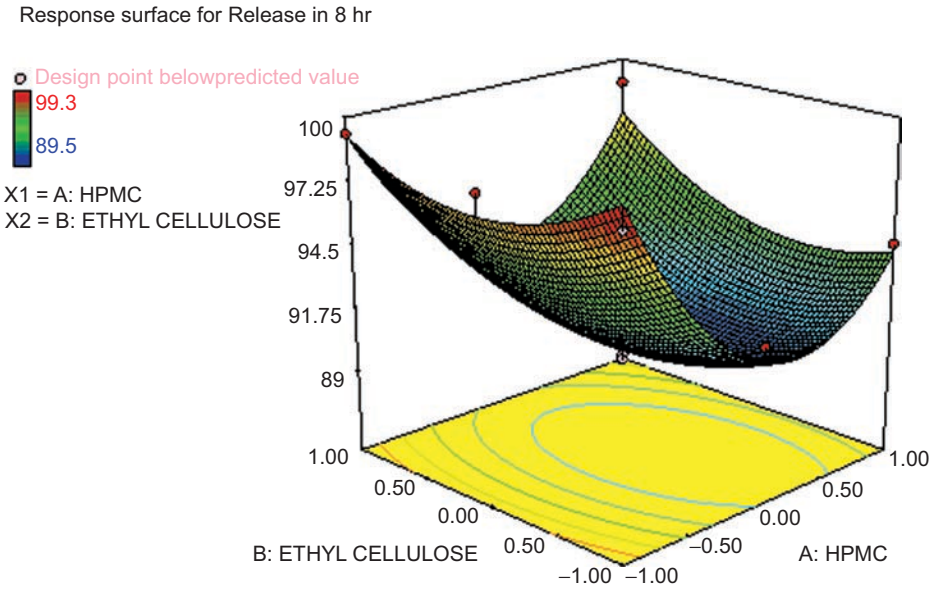


Figure 3. Response surface plot showing the effect of polymer composition on 'drug release in 8 h' ($Rel_{8h}$) from MS–SR matrix tablets.

Table 5. ANOVA for response $Rel_{8h}$

| Source | Sum of squares | df | Mean square | *F* value | *P* Value | Prob > *F* |
|---|---|---|---|---|---|---|
| Model | 161.31 | 5 | 32.26 | 17.90 | 0.0007 | Significant |
| A-HPMC | 18.73 | 1 | 18.73 | 10.39 | 0.0146 | |
| B-EC | 3.23 | 1 | 3.23 | 1.79 | 0.2219 | |
| AB | 3.24 | 1 | 3.24 | 1.80 | 0.2219 | |
| $A^2$ | 82.82 | 1 | 82.82 | 45.94 | 0.0003 | |
| $B^2$ | 10.78 | 1 | 10.78 | 5.98 | 0.0444 | |
| Residual | 12.62 | 7 | 1.80 | | | |
| Lack-of-fit | 9.39 | 3 | 3.13 | 3.87 | 0.1119 | Not significant |
| Pure error | 3.23 | 4 | 0.81 | | | |
| Cor total | 173.93 | 12 | | | | |

Coefficients with *p* value > 0.05 are not significant.

Table 6. Check point formulations (CPF) of MS, the predicted and the experimental values of response variable.

| Sl. No. | A; HPMC, mg | B; EC, mg | Predicted value of response | Experimental value of response | % Error |
|---|---|---|---|---|---|
| CPF1 | 22.15 | 9.25 | 90.35 | 89.98 | 0.41 |
| CPF2 | 22.00 | 9.00 | 90.24 | 91.20 | −1.06 |
| CPF3 | 21.90 | 9.15 | 90.19 | 90.07 | 0.13 |
| CPF4 | 22.00 | 9.15 | 90.24 | 89.98 | 0.29 |
| CPF5 | 22.10 | 9.20 | 90.32 | 90.89 | −0.63 |
| CPF6 | 21.95 | 9.35 | 90.25 | 89.12 | 1.25 |
| CPF7 | 22.05 | 8.80 | 90.25 | 89.67 | 0.64 |
| CPF8 | 21.95 | 8.85 | 90.20 | 90.12 | 0.09 |
| CPF9 | 21.80 | 9.00 | 90.15 | 90.43 | −0.31 |
| CPF10 | 22.20 | 8.65 | 90.32 | 90.67 | −0.38 |

physical appearance, drug content and release characteristics after storing at 25°C with 60% relative humidity (RH) and 40°C with 75% RH for 6 months[26].

## Biopharmaceutical evaluation

The *in vivo* study was performed following the guidelines of 'Committee of Purpose of Control and Supervision of Experiments on Animals (CPCSEA)', Ministry of Social Justice and Empowerment, Government of India, and approved protocol by the Institutional ethics committee. The *in vivo* studies were conducted on 18 adult healthy male New Zealand rabbits weighing 4.0–4.5 kg. Rabbits were acclimatized in animal house for 1 week and were fed a fixed standard diet. Eighteen rabbits were divided into three groups of six, each and were fasted for 24 h. The group I was fed with pure drug solution (PDS) of

25 mg MS in 5 mL purified water, group II was fed with prepared SR tablets (CPF8) equivalent to 25 mg of MS, and group III was fed with marketed SR tablets of MS 25 mg (EMBETA XR-25 tab). Water was allowed *ad libitum* during fasting and throughout the experiment. The rabbits swallowed the formulation without any difficulty. The matrix tablet was put behind the tongue to prevent its destruction due to biting. Blood samples (2 mL) were collected carefully from the marginal ear vein into heparinized centrifuge tubes at 0 h before dosing and then at 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 4.0, 6.0, 8.0, 10.0, and 12.0 h after administration of the tablets. The total blood collected from a rabbit did not exceed much more than the maximum safe bleed limit, i.e., 6.5–7.5 mL/kg body weight[27]. The withdrawn blood samples were transferred to a series of graduated centrifuge tubes containing 0.4 mL of 2.5% w/v sodium citrate solution. The samples were centrifuged at 2500 rpm for 5 min. The plasma was transferred into another set of sample tubes and frozen until assayed. One plasma sample (without dose of drug) was kept as blank. The sample was filtered through 0.25-µm membrane filter (Millipore). The MS concentration in blood plasma samples was analyzed by following HPLC method. A total 200 µL of plasma sample was mixed with 1 mL of acetonitrile, and then it was centrifuged. The supernatant was evaporated under nitrogen stream, and the residue was dissolved with 300 µL of the HPLC mobile phase, and then it was injected into the reverse-phase column (OSD-AM, 4.6 × 150 mm, YMC, Japan) of HPLC apparatus with UV detector. A mixture of phosphate buffer (pH 3, containing 0.5% triethylamine): methanol: acetonitrile (90:1:9) was used as mobile phase at a flow rate of 1.4 mL/min.

Table 7. Composition (%) of final optimized formulation (CPF8) of SR matrix tablet of MS, 25 mg.

| Name of components | % |
|---|---|
| Metoprolol succinate | 25 |
| HPMC K100M | 21.95 |
| Ethyl cellulose | 8.85 |
| DCP | 36.2 |
| HPMC E5 | 5 |
| Magnesium stearate | 2 |
| Aerosil | 1 |

### Pharmacokinetic study and statistical analysis

The data of plasma concentration of MS at different time intervals obtained by *in vivo* study was subjected to pharmacokinetic analysis to calculate various parameters such as maximum plasma concentration $C_{max}$; time to reach maximum concentration $T_{max}$ and area under the curve ($AUC_{0-\infty}$). The values of $C_{max}$ and $T_{max}$ were directly read from the plot of plasma concentration of MS vs. time (Figure 6). The $AUC_{0-\infty}$ was determined by means of trapezoidal rule. The relative bioavailability of MS from SR matrix tablet (CPF8) in comparison to PDS and marketed SR tablet was calculated by dividing its $AUC_{0-\infty}$ with that of PDS and marketed formulation. It required no dosage correction since each dose contained 25 mg of drug. Statistical analysis was performed by the Student's *t*-test and $P < 0.05$ was used to indicate statistical significance. The graphical correlation was developed by plotting the fraction of drug (MS) absorbed (FDA) from CPF8 in the *in vivo* study against the fraction of drug released in the *in vitro* study from CPF8 (Figure 7). Thus '*in vitro–in vivo* correlation' was developed.

## Results and discussion

### Pre-compression and post-compression parameters

The granules were first prepared according to the formula given in Table 1 and characterized with respect to size distribution, % fines, bulk density, tapped density, Hausner ratio, Carr's index, angle of repose, mass flow

Table 8. *In vitro* release kinetics of SR matrix tablets of metoprolol succinate.

| Formulation code | Zero order $R^2$ | First order $R^2$ | Higuchi $R^2$ | Korsmeyer–Peppas $R^2$ | Korsmeyer–Peppas release exponent ($n$) |
|---|---|---|---|---|---|
| CPF8 | 0.9720 | 0.8410 | 0.9872 | 0.9798 | 0.8132 |

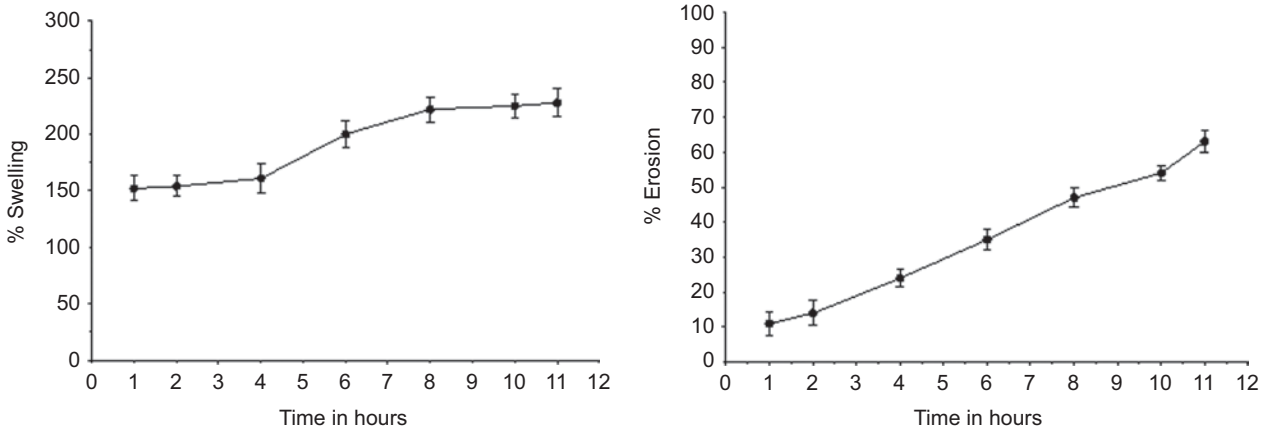


Figure 4. Swelling-eroding behavior of optimized batch of matrix tablet CPF8. Data are represented as mean ± SD ($n = 3$).

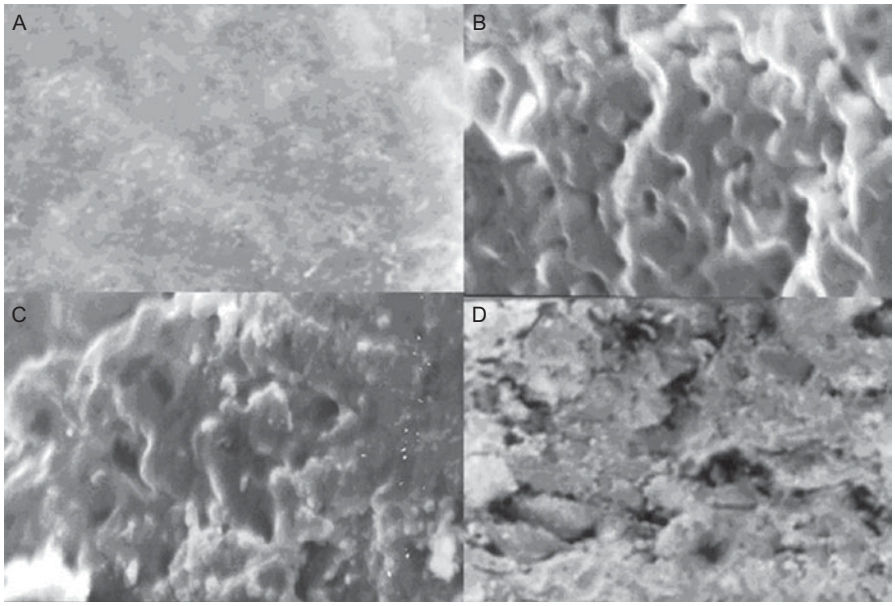


Figure 5. SEM photomicrographs of optimized SR matrix tablets of metoprolol succinate (CPF8) showing surface morphology after 0 h (A), 2 h (B), 5 h (C), and 10 h (D) of dissolution study.

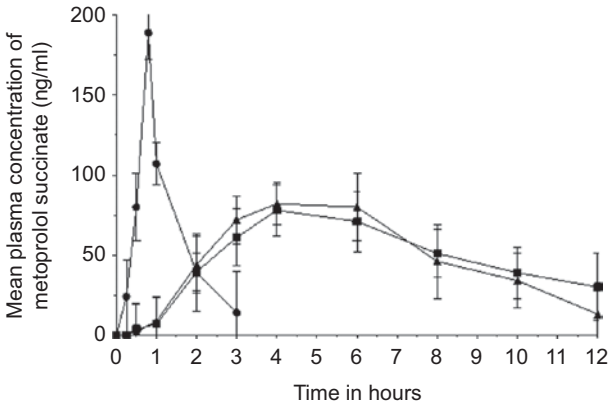


Figure 6. Mean (±SD) plasma concentration of metoprolol succinate in male 'New Zealand rabbits' ($n=6$) following oral administration of reference standard (PDS) (•), SR matrix tablets (CPF8) (■) and marketed SR matrix tablets (▲).

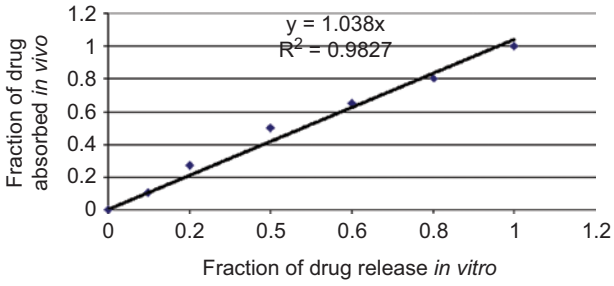


Figure 7. Correlation of 'Fraction of drug absorbed' *in vivo* and 'Fraction of drug release' *in vitro* for the sustained release matrix tablets of metoprolol succinate.

rate (Table 2). Angle of repose was less than 30° for all the batches of granules indicating satisfactory flow behavior. The tablets of different batches were subjected to various evaluation tests, such as weight variation, friability, hardness, and content uniformity according to the procedure specified in USP 30. The weight variation and friability were not more than 2% and 0.7%, respectively. Drug content was found uniform among different batches of the tablets, and the drug content was within 98–102% (Table 3). The dissolution studies of all formulations, as shown in Figures 1 and 2 indicated that formulation $H_i$ is the best option for further optimization of composition. This showed low value of bulk density, low angle of repose, minimum friability and maximum MDT and good control on flowability. It extended the release of drug up to 12 h. So, formulation $H_i$ was considered suitable for further studies.

Figures 1 and 2 depict the dissolution profiles of MS from hydrophilic matrix tablets containing 30% polymer (Batches $A_i$–$J_i$). Drug release was almost complete in about 4 and 5 h, respectively in case of $A_i$ and $F_i$. Faster release of the drug from the hydrophilic matrix ($A_i$ and $F_i$; 30% HPMC) was probably due to gel effect, erosion effect and faster dissolution of the water-soluble drug from the core, and drug's diffusion out of the matrix creates the pores, which are further filled by the entry of solvent molecules. Its burst release (%) is also high. Matrix systems ($E_i$ and $J_i$) containing higher fraction of EC in comparison to HPMC showed higher release rate and could not control release rate. Diffusion of soluble drug through hydrophobic material is retarded due to its low water permeability. However, the soluble molecules easily diffuse out through the cracks/pores formed in the matrix dominated by hydrophobic polymer, and these cracks are not sufficiently filled by its swelled gel because EC has less gel effect. Release period may be extended further by appropriate blending of polymers (EC and HPMC K100M) which comprises of lower percentage of EC in comparison to HPMC. Formulations $C_i$

and $H_i$ containing EC (10%) and HPMC (20%) showed maximum delayed release in each category of filler, i.e., displayed in Figures 1 and 2, respectively. Possibly swelled gel of HPMC packs sufficiently the aforementioned cracks. In Figures 1 and 2 formulations $B_i$, $D_i$, $C_i$ and $G_i$, $I_i$, $H_i$ had shown controlled release according to the polymer combination and type of fillers. The insoluble excipients can delay the dissolution rate owing to less wetting ability and permeability. The water insoluble filler, DCP, extended release period more in comparison to water-soluble filler lactose. By comparing release profiles of all the batches, it is apparent that HPMC in the mixed matrix tablets had increased the drug release rate while EC acted as release retardant. The matrix (batch $H_i$) released the drug up to 12 h. A close examination of release profile indicates that incorporation of EC and HPMC K100M in the range of 5–15% and 15–25%, respectively may be appropriate ranges for experimental design.

## Analysis of ANOVA, model equation and response surface plot

The fit summary (Table 5) for $Rel_{8h}$ of MS suggested the quadratic relationship where some of the additional terms were significant ($p \leq 0.05$). A quadratic model explained 92.75% $Rel_{8h}$ which indicates 7.25% of the total variation could not be explained by the model. The regression equation represented best description of response after the nonsignificant parameter ($P > 0.05$) was eliminated from the result as summarized in Table 5. The lack-of-fit $F$ value (3.87) indicated nonsignificance ($P > 0.05$) as desired. There is 11.19% chance that lack-of-fit value occurs due to noise. The ANOVA result showed only main effect (A, HPMC), the quadratic effect of $A^2$ and $B^2$. The interaction effect of two polymers ($A*B$) was found insignificant ($P > 0.05$). The other adequacy measures are $R^2$ (0.9275), adjusted $R^2$ (0.8756) though predicted $R^2$ (0.4399) is not close to the adjusted $R^2$. The adequate precision (10.289) indicated an adequate signal to noise ratio. Following equation is obtained after deleting insignificant terms from ANOVA results. In this case $A$, $A^2$, $B^2$ are significant model terms.

$$Rel_{8h} = 90.21 - 1.77A + 5.48A^2 + 1.98B^2$$

The negative regression coefficient on A implies that an increase in the factor A (HPMC) causes decrease in % release within the studied levels. As a main factor, B has no significant effect. However, the effect of its quadratic terms on the response explains that $Rel_{8h}$ increased both at lower and higher values of $B$ indicating less control on % release. When it approaches center value, drug release was found retarded. Release rate was retarded as it approaches center value because release (%) is low. This is evident from response surface plot (see Figure 3). In this model, absolute values of regression coefficients of variables are comparatively lower, and intercept value is very high. High $R^2$ value and model $F$ value (17.9) indicate that the model is adequate and significant. $Rel_{8h}$ is adequately represented by the model equation. Predicted response values were in good agreement with the experimental response values as obtained from the 'check point formulations' (see Table 6). Optimum value of response is in the range of 89.5–90.5. The formulation CPF8 as shown in Table 7 was found as the best optimized formula for MS–SR as the % error was found minimum.

## Discussion on drug release mechanism in tablet, swelling and surface topography of tablet

From the study of release kinetics of CPF8, we found that this formulation conforms much to Higuchi model ($R^2 = 0.9872$) and Korsmeyer–Peppas model ($R^2 = 0.9798$). Value of release exponent "$n$" was found to be 0.8132. The value of "$n$" was found to vary with type and concentration of polymers. Release of drug from the matrix tablet generally follows diffusion for water-soluble drug and erosion or relaxation for water insoluble drug. Here, drug release follows both diffusion and erosion mechanism. Gravimetric evaluation of hydration and mass loss due to erosion in CPF8 tablet revealed the water-uptake capacity of matrix tablet (Figure 4). It is expected that erosion of matrix in CPF8 tablet will be less because it consisted of filler DCP. As lactose is a water-soluble excipient, it facilitates more penetration of water into the matrix and erosion of matrix in comparison to DCP. HPMC based matrix tablet does not disintegrate and remains intact in the media owing to swelling of polymer.

Figure 5 shows the photographs of matrix tablets (CPF8) by scanning electron microscope. SEM photographs of the tablets revealed that gelled matrix was intact and pores were formed throughout the matrix owing to erosion. Erosion of outer layer and pore diameter increased with time of dissolution as shown in Figure 5-a to Figure 5-d, where times of erosion are 0, 2, 5 and 10 h, respectively. Hence, the formation of both pores and gelling structure in tablets indicated the involvement of both erosion and diffusion mechanisms to be responsible for sustaining the release of MS from the formulation.

## Stability studies

The formulations after storing at 25°C/60% RH and at 40°C/75% RH for 6 months showed no change in physical appearance or dissolution pattern. The results of the stability studies suggested that the formulations might provide a minimum shelf life of 2 years[28].

## Bioavailability studies of MS

After oral administration of PDS 25 mg, SR matrix tablets (CPF8) 25 mg and marketed SR matrix tablets (EMBETA XR-25 tab), the *in vivo* data were obtained, and these were plotted against time in Figure 6. The pharmacokinetic parameters $C_{max}$, $T_{max}$ and $AUC_{0-\infty}$ were summarized in Table 9. The pharmacokinetic parameters $T_{max}$ and $AUC_{0-\infty}$, are related to the rate and extent of absorption, respectively, while $C_{max}$ is related to both the processes. The extent of absorption is a key characteristic of a drug

Table 9. Mean (±SD) pharmacokinetic parameters of metoprolol succinate in 'New Zealand rabbits' ($n = 6$), orally administered with pure drug solution (PDS) 25 mg, SR matrix tablets (CPF8) 25 mg and marketed SR matrix tablets (EMBETA XR-25 tab).

| Pharmacokinetic parameter | Reference standard (PDS) | Test formulation SR matrix tablet (CPF8) | Reference formulation marketed SR matrix tablet |
|---|---|---|---|
| Peak plasma concentration, $C_{max}$ (ng/mL) | 189 ± 17 | 78 ± 16 | 82 ± 13 |
| Time to reach plasma concentration, $T_{max}$ (hours) | 0.8 ± 1.17 | 4.1 ± 0.93 | 4.0 ± 0.87 |
| Area under the curve $AUC_{0-\infty}$ (ng/mL/h) | 1373 ± 457 | 2387 ± 642 | 2265 ± 463 |

Significant at $P < 0.05$.

formulation, and therefore $AUC_{0-\infty}$, is an important parameter for analysis in a comparative bioavailability study. It is evident from Figure 6 that PDS could produce no sustained effect. The formulated matrix tablet (CPF8) showed significantly lower $C_{max}$ than PDS, and it required more time (4.1 ± 0.93 h) to reach $C_{max}$ (78 ± 16 ng/mL) as compared with PDS ($T_{max}$ 0.8 ± 1.17 h). The area under the curve increased nearly 1.7 times higher in CPF8 than PDS. $C_{max}$ and $T_{max}$ values of formulated CPF8 and marketed SR matrix tablets were comparable, and $AUC_{0-\infty}$ of formulated CPF8 was higher than the marketed SR matrix tablets. These pharmacokinetic parameters (lower $C_{max}$ and prolonged $T_{max}$) indicated that drug release maintained smooth extended absorption of drug and sustained pseudo-steady state concentration of MS in plasma level with minimal fluctuations up to 12 h. However, there was a lag time of approximately 1–2 h before blood levels could be measurable.

Next, 'fraction of drug absorbed' *in vivo* was plotted against 'fraction of drug released' *in vitro* keeping time as common factor in Figure 7. A linear correlation passing through origin was obtained ($R^2 = 0.9827$), indicating that *in vivo* absorption data were consistent with the *in vitro* release data of matrix system (CPF8). Controlled release formulations of MS providing consistent plasma concentration without high peaks are more likely to have effects on $\beta_2$-receptors due to loss of $\beta_1$-specificity[29,30].

## Conclusions

Results of this study demonstrated that combination of both hydrophilic and hydrophobic polymers could be successfully employed to formulate SR matrix tablets of Metoprolol Succinate. Development of cellulose-based matrix tablet is made through preparation, characterization, dissolution study, experimental design and bioavailabilty study. The new SR matrix tablet (CPF8, 25 mg) sustained the release of drug up to 12 h. The successful outcome of the present study warrants for further studies in human volunteers to assess the ability of the above matrix tablet of MS in order to achieve effective and safe therapy in hypertension.

## Declaration of interest

The authors report no declarations of interest.

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