Mangesh R Bhalekar
Department of Pharmaceutics,
AISSMS College of Pharmacy,
Pune, Maharashtra, India

Ashwini R Madgulkar
Department of Pharmaceutics,
AISSMS College of Pharmacy,
Pune, Maharashtra, India

Anil V Kadam
Department of Pharmaceutics,
AISSMS College of Pharmacy,
Pune, Maharashtra, India

Formulation and evaluation of sustained release matrix tablet of metoprolol succinate

Mangesh R Bhalekar, Ashwini R Madgulkar and Anil V Kadam

Abstract

Metoprolol succinate, a BCS class I drug and selective β1 receptor blocking agent used in treatment of hypertension and angina pectoris. The objective of the present study was to develop sustained-release matrix tablets of metoprolol succinate by using different grades of eudragit (Eudragit RSPO, Eudragit RLPO) along with HPMC K15. Here, hydroxylpropylmethylcellulose was used to control burst release. Eudragit RSPO having low permeability in water.so it gives better sustained action. The tablets were prepared by the wet granulation method. The compressed matrix tablets were evaluated for various parameters like hardness, friability, weight variation, drug content uniformity, drug-polymer interaction and *in-vitro* drug release studies. In-vitro drug release studies were performed in pH 6.8 phosphate buffer using US Papparatus-II (paddle) at 100 rpm for 12 hrs.

Keywords: Metopropol succinate, Eudragit RSPO, Eudragit RLPO, Sustained release, matrix tablet

1. Introduction

Metoprolol succinate is a Beta 1-selective (cardio selective) adrenoceptor blocking agent belonging to class I according to the Biopharmaceutics Classification Scheme (BCS) [1]. The half-life of drug is relatively short approximately 4-6 h and in normal course of therapy drug administration is required every 4-6 h, thus warrants the use of sustained release formulation for prolong action and improved patient compliance [2].

Popular method to sustain drug delivery is use of hydrophilic polymers [3-5]. Earlier reports regarding sustained release formulations of metoprolol have employed various hydrophillc polymers such as Eudragit, HPMC in various grades and combinations [6]. One of the work cited in literature has used combination of Eudragit and HPMC [6]. it is well known that the polymers in combination provide rheological synergism which enables the sustained release in lesser quantity of polymer [7, 17]. The exact quantitative combination of polymers to achieve desired response can only be worked out in minimum effort only by use of statistical Design of experiment approach [8]. Hence, the present work was undertaken to optimize the quantity of polymers Eudragit RSPO and Eudragit RLPO in a sustained release metoprolol matrix tablet. A two factor three level design has been employed to optimize the release at 2nd and 8th hour in a 12 h release profile.

2. Material and methods

Materials that are used throughout the experiment are metoprolol succinate (Intas pharmaceuticals, Ahmedabad), Eudragit RSPO, Eudragit RLPO (Evonik Degussa India Pvt. Ltd. Mumbai), remaining all excipient obtained from local suppliers.

2.1 Drug-excipient compatibility study

The drug-excipient interaction was studied by FTIR spectrocopic technique. Metoprolol succinate and its mixture with Eudragit RSPO, Eudragit RLPO and HPMC K15M were separately stored at elevated temperature (40°C) for two weeks and IR spectra were recorded by using Shimadzu, (miracle IR affinity-1) spectrophotometer between wavelength 300-3000cm^{-1}.

2.2 Formulation of matrix tablet

Matrix tablets of Metopropol Succinate were prepared by wet granulation techniques, using varying proportion of Eudragit polymers in combination.

Correspondence
Mangesh R Bhalekar
Department of Pharmaceutics,
AISSMS College of Pharmacy,
Pune, Maharashtra, India

Metopropol Succinate (50 mg), required blend of Eudragit RSPO and RLPO grades, HPMC (K15M), lactose and magnesium stearate was mixed thoroughly and granulated by using solution of isopropyl alcohol, the prepared mass was sieved by using sieve no.16 and subjected to compression on *Rimek Mini press II MT* tablet press make Karnavati using B tooling at constant pressure. Before going for granulation, prepared powder blend was suitably lubricated and subjected to precompression analysis such as bulk density, tapped density, compressibility index, angle of repose were determined by standard procedures reported in literature [9].

2.3 Experimental Design
A 2^3 full factorial design was employed as per the standard protocol. The amounts of Eudragit RSPO (X_1) and Eudragit RLPO (X_2) were selected as the factors, studied at 3 levels each. All other formulation and processing variables were kept invariant throughout the study. Table 2 summarizes an account of the 9 experimental runs studied, their factor combinations, and the translation of the coded levels to the experimental units employed during the study. 2nd hr release, 8th hr release and t50% was taken as the response variables [6].
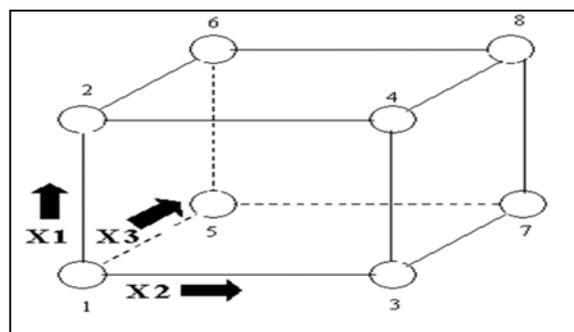

Fig 1: 2^3 Full factorial Design

Table 1: Factorial Design Data

Independent Variable	Coded Units	Levels			Response (R1)	Drug Release (%)	Response (R2)	Drug Release (%)	Response (R3)	t50 (%)
		-1	0	+1						
Eudragit RSPO	X1	10	15	20	Release at 2nd h	19.87	Release at 8th h	68.92	t50(2^{nd}h)	9.93
Eudragit RLPO	X2	10	15	20					t50(8^{th}h)	34.46

2.4 Experimental runs
All data are were inserted into the design expert software version and we get 9 optimization runs as given in the table 2 [10].

Table 2: composition of optimization trial runs (all quantities in mg)

Formulation code	Metoprolol succinate	Eudragit RSPO	Eudragit RLPO	HPMC K15M	Lactose	Magnesium stearate
F1	50	10	10	05	50	05
F2	50	10	15	05	50	05
F3	50	10	20	05	50	05
F4	50	15	10	05	50	05
F5	50	15	15	05	50	05
F6	50	15	20	05	50	05
F7	50	20	10	05	50	05
F8	50	20	15	05	50	05
F9	50	20	20	05	50	05

2.5 Pre compression analysis
The tablets are analyzed for Bulk density, tapped density, compressibility index, Hausner's ratio, angle of repose as per procedure reported in literature [9].

2.6 Post compression analysis
The tablets are analysed for weight variation, hardness, thickness, friability, drug content as per procedures reported in litereature [9, 12].

Drug content
Twenty tablets were triturated and the quantity of powder equivalent to 50 mg of metoprolol is accurately weighed and transferred to 100ml of volumetric flask and extracted with phosphate buffer pH 6.8.then, keeping in sonicator for 2 h. Then Solution was filtered, suitably diluted and absorbance was measured at 223 nm using double beam UV spectrophotometer (LABINDIA UV-3000) against phosphate buffer as blank [13].

In vitro drug release studies
The USP II paddle apparatus was used with 900 ml of Gastric fluid (pH 1.2) for 2 h. After 2 h the dissolution media was changed i.e. Intestinal Fluid (pH 6.8), this is for 3 h. Then after that, change the dissolution medium to phosphate buffer (pH 6.8) at 37° C and 50 rpm. Samples (5 ml) were withdrawn at 1, 2, 3, 4, 5, 6, 8, 10, 11 and 12 h and were assayed spectrophotometrically at respective λ max (223nm). From the absorbance values, the percent cumulative release of metoprolol was calculated [14]. (n=6)

2.7 Kinetic Modelling
The dissolution profile of all the batches was fitted to various models such as first order, zero-order, Higuchi and Korsmeyer and Peppas, to ascertain the kinetic modeling of drug release [15].

2.8 Optimization and validation of statistical model
The responses from release data were fed to design expert 10.1 trial version and the equations were generated to predict responses release at 2h and release at 8 h. The numerical optimization was done using desirability function and the predicted formula were prepared analyzed to test the prognostic abilities of the formula.

3. Result and discussion

3.1 Calibration curve of metoprolol succinate

The standard graph of metoprolol succinate showed a good linearity in 0.1N HCl ($R^{2=}$ 0.9983), and in phosphate buffer 6.8 ($R^{2=}$ 0.9953) in the concentration range of 0-30 µg/ml. The equation of line were

-Y = 0.1269X + 0.0276--HCL (0.1N) Y=0.0281X+0.0845 -P.B (6.8)

3.2 Drug-excipient compatibility

Major peaks of metoprolol were retained in the combination spectra and no new peak was observed in graph (fig 2) and hence it was concluded that metoprolol was compatible with the polymers Eudragit and HPMC. (Table 3)
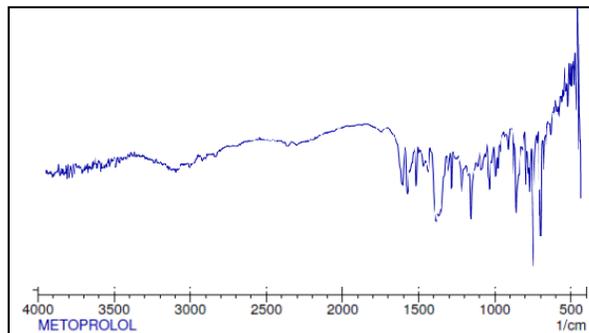

Fig 2: FTIR spectra of Metoprolol

Table 3: Characteristic peaks of pure Metoprolol succinate

Sr.no.	Type of bond	Type of vibrations	Actual frequency(Cm$^{-1)}$	Observed frequency(Cm$^{-1)}$
1	C=C	Stretching	~1600	1598.99
2	N-H	Stretching	3310-3140	3211.48
3	C-O	Stretching	1350-1260	1294.24
4	C-O	stretching	1150-1070	1095.57
5	C-O	stretching	1410-1300	1321.24

3.3 Precompression studies

Precompression parameters such as bulk density, tapped density, compressibility index, angle of repose were measured and the results are shown in table 4.

Table 4: Precompression parameters

Formulations	Bulk density	Tapped density	Compressibility index	Hausner's ratio	Angle of repose
F1	0.450	0.272	8.08	1.15	26.64
F2	0.445	0.262	6.79	1.16	28.42
F3	0.445	0.270	9.25	1.11	30.90
F4	0.445	0.272	9.92	1.12	25.30
F5	0.445	0.268	8.58	1.15	30.21
F6	0.446	0.276	10.86	1.14	26.52
F7	0.446	0.275	10.54	1.12	27.54
F8	0.445	0.272	9.92	1.12	28.51
F9	0.441	0.268	10.07	1.14	29.28

(n=3)

Bulk density ranged between 0.441-0.450 which is good for compression. The CI was between 6.79 - 10.86 and angle of repose was between 25.30- 30.90 which indicates good flow.

3.4 Post compression analysis

Post compression analysis, such as weight variation, hardness, thickness, friability, and drug content as per the standard procedure reported in literature were carried out and results are shown in table 5.

Table 5: Post compression parameters

Formulation code	Weight variation (mg)	Hardness (kg/cm2)	Thickness (mm)	Friability (%)	Drug content (%)
F1	130±2	6.5	3.25	0.19	97.26±0.85
F2	135±2	5.7	3.28	0.25	98.34±0.92
F3	138±3	6.7	3.36	0.33	98.67±0.36
F4	135±2	5.5	3.60	0.27	98.33±0.68
F5	130±2	7.2	3.56	0.28	98.12±0.15
F6	145±3	6.0	3.47	0.37	99.67±0.77
F7	140±2	6.2	3.30	0.25	98.47±0.33
F8	145±3	7.0	3.45	0.26	97.43±0.72
F9	150±3	6.5	3.50	0.30	97.64±0.28

(n=3)

Hardness ranges between 5.5 to 7.2 is good for sustained release matrix tablets, friability between 0.19 to 0.37% which is within prescribed limits, drug content was found between 97.67 to 99.67% which is compliant with tolerance given in USP [18].
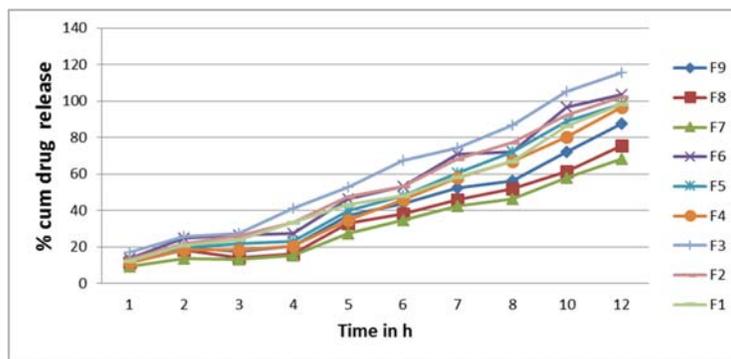
3.5 *In vitro* drug release profile

Fig 3: cumulative % drug release of nine batches of experimental design

3.6 Kinetic modeling of drug release
The dissolution profile of all the batches was fitted to various models such as zero-order, first order, Higuchi and Korsmeyer and Peppas, to ascertain the kinetic modeling of drug release and their results are mentioned in table 6 [15].

Table 6: Kinetic modeling indicating best fit model

Formulation	Zero order	First order	Peppas	Matrix	Hixson-Crowell	Best fit model
	R^2	R^2	R^2	R^2	R^2	
F1	0.9665	0.9666	0.9724	0.9634	0.9666	Peppas
F2	0.8674	0.8676	0.7661	0.8693	0.8676	Matrix
F3	0.9469	0.9469	0.9824	0.9822	0.9471	Peppas
F4	0.9552	0.9554	0.9614	0.9690	0.9553	Matrix
F5	0.9644	0.9646	0.9673	0.9670	0.9645	Peppas
F6	0.9406	0.9409	0.9755	0.9797	0.9408	Matrix
F7	0.9113	0.9116	0.9628	0.9854	0.9115	Matrix
F8	0.9090	0.9093	0.9535	0.9820	0.9092	Matrix
F9	0.9295	0.9297	0.9628	0.9804	0.9296	Matrix

Peppas model is best suitable for the formulations F1, F3, F5 while formulation F2, F4, F6, F7, F8, F9 showed Higuchi as a best fit model which may be attributed to their compositions as given in table 6.

3.7 Optimization equation
The optimization runs and responses are tabulated in table 7.

Table 7: Optimization Runs and responses

Formulation code	Metoprolol succinate	Eudragit RSPO	Eudragit RLPO	Hpmc K15M	Lactose	Magnesium stearate	R1 Cum Drug release 2 h (%)	R2 Cum Drug release 8 h (%)
F1	50	10	10	05	50	05	20.79	67.10
F2	50	10	15	05	50	05	21.79	77.38
F3	50	10	20	05	50	05	25.56	86.76
F4	50	15	10	05	50	05	18.47	66.98
F5	50	15	15	05	50	05	19.48	72.11
F6	50	15	20	05	50	05	24.77	71.91
F7	50	20	10	05	50	05	13.47	46.14
F8	50	20	15	05	50	05	18.47	51.66
F9	50	20	20	05	50	05	19.52	51.16

All the weights of ingredients are taken in mg.

Different polymers such as Eudragit RSPO, Eudragit RLPO and cellulose derivatives such as HPMC K15M have been used as release retarding agents. Eudragit helps to give better control over drug release from tablet over a longer period of time. HPMC K15M is also used to control the initial burst release of tablet.it was kept constant for all formulation batches.

The equations obtained for the 3^2 design for Release 2h and Release 8h were as follows:

1) For 2nd h release
$+20.63 - 2.59 * A + 2.27 * B + 1.66 * AB - 2.26 * A^2 + 0.41 * B^2$ --- (Equation 1)

2) For 8th h release
$+71.14 - 12.88 * A + 5.77 * B - 2.41 * AB - 6.13 A^2 - 1.21 * B^2$ --- (Equation 2)

The equations and the response surface fig show a predominant retardation of drug release with Eudragit RSPO while the increase in RLPO improved the release because it having high penetration of water and Eudragit RSPO having less solubility in water and hence, water penetration is low. Together the different polymers actually retarded the release which may be attributed to rheological synergism between the polymer grades.

Goal setting was done based on literature [2] and at goal for 2nd h release was between 20-25% and for 8th hr release it was > 60%.
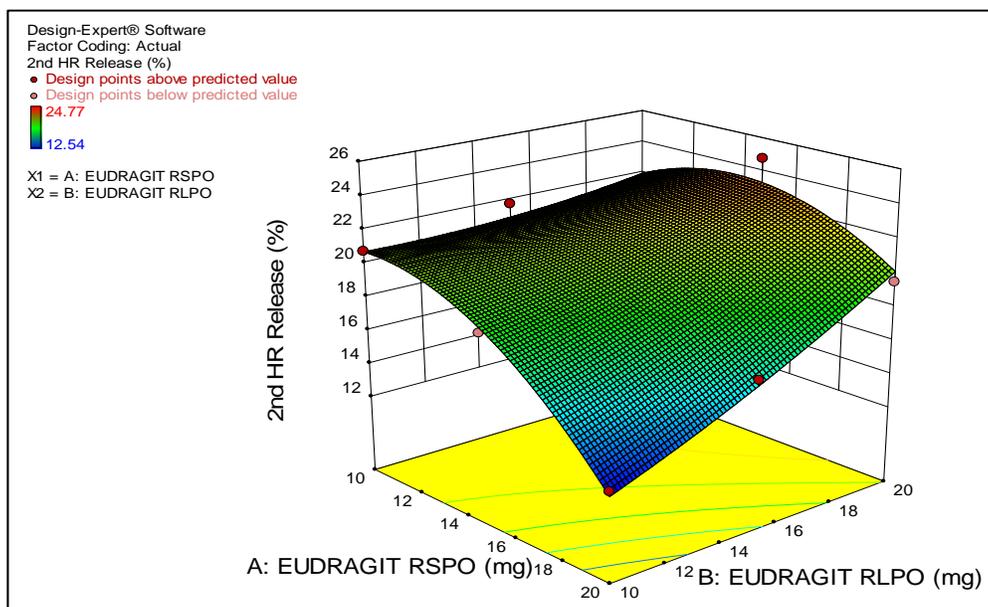
3.8 Response surface plot
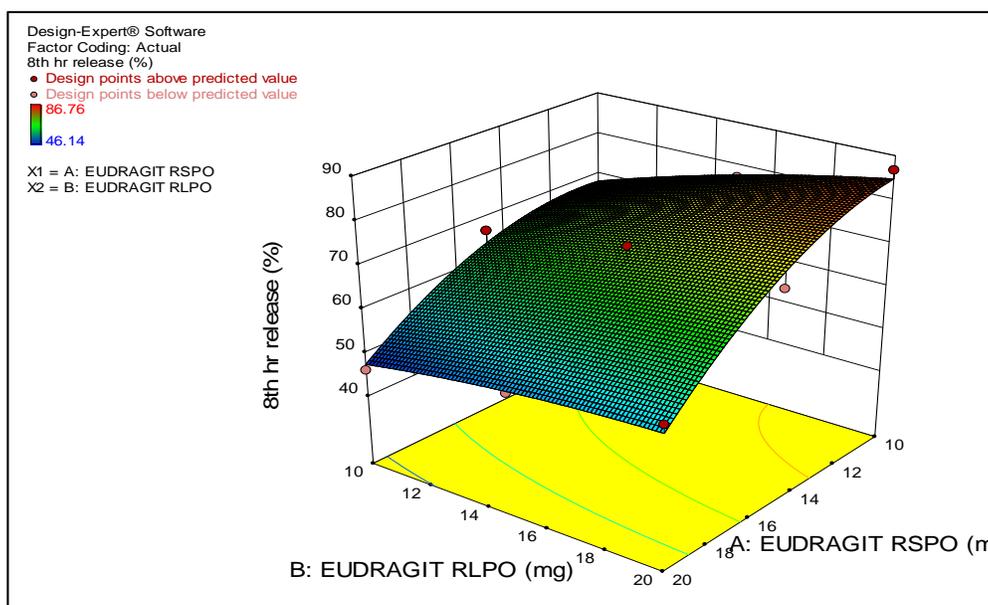

Fig 3: 3D response surface plot (2nd hr)

Fig 4: 3D response surface plot (8th hr)

The tablets were prepared using the optimized formula (table 8) and evaluated for drug release. The results show appreciable agreement between the predicted and observed values. Table 9 with low % error this shows the prognostic abilities of the model are robust and hence model is validated.

Table 8: Composition of optimized batch

Ingredients	Quantity in mg
Metoprolol Succinate	50.00
Eudragit RSPO	15.60
Eudragit RLPO	14.40
HPMC K 15M	5.00
Lactose	5.00
Magnesium stearate	5.00
Total	140.00

Table 9: Validation of model

Optimized formulation	Response variable	Experimental value	Predicted value	Percentage prediction error	Desirability
	Y1	19.87%	20%	0.65	1.02
	Y2	68.92%	68.80%	-0.17	0.98

Here, Y1: Response at 2nd hr, Y2: Response at 8th hr

3.9 Similarity factor determination
Comparative dissolution profile of optimized formulation Test and marketed formulation was carried out and f 2 was found to be 90.4 which indicates the good similarity between test and reference products. Formula for similarity factor determination.

$$f_2 = 50 \times \log\left\{ \left[1 + (1/n)\sum_{j=1}^{n}|R_j - T_j|^2 \right]^{-0.5} \times 100 \right\}$$

4. Conclusion
Metoprolol succinate sustained release matrix tablets were prepared successfully using Eudragit polymer of different viscosity (Eudragit RSPO and Eudragit RLPO) by using wet granulation techniques. The hydrophilic matrix of HPMC K15M alone could not control the drug release. Prepared tablet of metoprolol succinate release the drug effectively for 12 hours. It is evident from the results that a matrix tablet prepared with HPMC K15M and a Eudragit Polymers is a better system for sustained release of a highly water-soluble drug like metoprolol succinate. From the above study it was concluded that, formulation with desired drug release achieved with combination of Eudragit RLPO and RSPO, appropriate balancing between various levels of these two polymers may contributes better release. High degree of prognosis obtained using RSM corroborates that a 2^3 factorial design is quite efficient in optimizing drug delivery systems. Hence, from the study it was concluded that prepared matrix tablet can sustained release upto 8 to 12 hrs.

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