RESEARCH ARTICLE

Optimization of metoprolol tartrate modified-release matrix tablet formulation using Eudragit NE as binder for metoprolol fluid bed granulation

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The aim of this experimental work was to investigate the possibility of obtaining hydroxypropyl methylcellulose (HPMC) hydrophilic matrix extended-release dosage forms with metoprolol by using aqueous dispersions of Eudragit NE, as binders in fluid bed granulation. To evaluate the influence of formulation variables (levels of HPMC—Methocel K100 M and Surelease E7 19010) on drug release during a period of time of 12 hours, and on the kinetic release, a full factorial experimental design with two factors and three levels was used. The formulation factors were the granulation polymer concentration and the matrix-forming polymer concentration. The obtained results have shown that the percentage of the drug released during the 12 hours is influenced both by the Methocel ratio and the Eudragit NE ratio; increasing the ratios of Eudragit and Methocel leads to the decrease of the percentage of the released drug. The influence of Eudragit NE percentage is maximum at four and six hours, but the influence of Methocel K100 M concentration is almost the same at all sampling times; all studied formulations showed a kinetic release that fitted best with the Peppas model.

***Key words*:** *Eudragit NE, extended release, fluid bed granulation, hydrophilic matrix, metoprolol*

INTRODUCTION

Metoprolol is a cardioselective antagonist of the β-adrenergic receptors (β-blockers) used for the treatment of cardiovascular diseases. Due to the short half-life (3–5 hours), metoprolol is currently used in extended-release dosage forms.[1,2] Various types of oral extended-release dosage forms are currently in use. Among these, the matrix offers the simplest approach to designing a sustained-release system. Hydrophilic matrix is the most commonly used method to obtain extended-release dosage forms, and cellulose ethers such as hydroxypropyl cellulose (HPC) and hydroxypropyl methylcellulose (HPMC) are extensively used. HPMC is available in different grades based on the relative substitution of hydroxypropyl and methoxyl groups with different hydration rates (i.e., gel formation rate) and it is used as a matrix-forming polymer in the preparation of modified-release dosage forms.[3] Eudragit NE 40D is an aqueous dispersion of a neutral copolymer based on ethyl acrylate and methyl methacrylate used for modified-release drugs.[4-6] It can be used as a binder, together with the hydrophilic polymer for matrix formation.[7]

Highly water-soluble drugs (such as metoprolol) formulated in hydrophilic matrix may be characterized by an initial burst effect.[1] Development of extended-release dosage formulations must overcome the high solubility of metoprolol, which produces a too rapid drug release. The solution consists in formulations that ensure a gradual release of the drug during the desired time period. This goal can be achieved by using retardation polymers or polymer blends.[8] Mixture of the granules of highly water-soluble drugs obtained via fluid bed granulation using water-insoluble coating

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polymers as binders in combination with high-viscosity HPMC as matrix forming could circumvent this problem. Because metoprolol tartrate is more soluble in water than metoprolol succinate, we preferred to use metoprolol tartrate in the studies. Many studies were reported regarding the development of extended-release formulations with metoprolol tartrate.[9-11]

The purpose of this study was to evaluate the influence of formulation variables (ratios of HPMC—Methocel K100 M and Eudragit NE) on drug release from tablets, during a period of 12 hours, and on the kinetic release to overcome the burst effect of metoprolol in hydrophilic matrix extended-release dosage forms.

MATERIALS AND METHODS

Materials

Metoprolol tartrate (Microsin, Romania); lactose monohydrate 200 mesh (Meggle, Germany); HPMC: Methocel K100 M (Colorcon, UK); lactose DC (DC: directly compressible): Tabletose 80 M (Meggle, Germany); silicon dioxide: Aerosil 200 (Degussa, Germany); magnesium stearate (Merck, Germany); Eudragit NE 40D (Degussa, Germany).

Experimental design

To perform the study, a full factorial experimental design with two factors and three levels was used. The independent variables (formulation and process variables) are shown in Table 1. The experimental design matrix is shown in Table 2. Construction of the experimental design, computation of coefficients, statistical parameters, and fitting of the experimental data to assess the results were performed using Modde 9.0 software, Umetrics, Sweden.[12]

Preparation of granules

The granulation process was performed in a fluid bed granulator (Aeromatic AG, Switzerland). The granulation formula is presented in Table 3 and the working conditions are presented in Table 4. After ending the atomization of the binder solution, the granules were dried for 30 minutes in the same apparatus at 60°C. Eudragit NE 40D was used as a binder in aqueous dispersions of different concentrations (4, 8, and 12%; each added separately).

Preparation of tablets

Compression of the obtained granules was achieved by an eccentric tablet press (Korsch EK0, Germany), equipped with a 10 mm diameter lenticular set punch. The tablets mass was fixed at 450 mg corresponding to a concentration of 100 mg metoprolol tartrate/tablet. The tableting formula contains metoprolol granules 50%, silicon dioxide 1%, magnesium stearate 1%, Methocel K100 M in ratios of 20-40%, and lactose weighing the difference, according to the experimental design.

Table 1: Independent variables (formulation and process variables)

Variables	Symbols	Levels		
		-1	0	+1
Eudragit ratio (%)	X_1	4	8	12
Methocel ratio (%)	X_2	20	30	40

Table 2: Matrix of the experimental design

Experiment name	Run order	X1	X3
N1	2	4	20
N2	7	4	30
N3	4	4	40
N4	8	8	20
N5	10	8	30
N6	9	8	40
N7	5	12	20
N8	11	12	30
N9	3	12	40
N10	6	4	30
N11	1	4	30

X_1: Eudragit ratio, X_2: Methocel ratio

Table 3: Granulation formula

	% (m/m)
Metoprolol tartrate	27,78
Lactose monohydrate	30
Eudragit NE 40D*	4-8-12
Distilled water**	q.s.

*According to the experimental design shown in Table 1 **required for the preparation of a binder solution with 26% polymer

Table 4: Working conditions

Solution spray rate or flow: Peristaltic pump (rpm)	10
Nozzle diameter (mm)	0,8
Atomization pressure (atm.)	1
Air volume (m^3/min)	3–5
Inlet air temperature (°C)	70
Outlet air temperature (°C)	27–33
Spraying duration (min)	25

Determination of the dependent variables (responses)

The dependent variables were the percentage of metoprolol tartrate released at different times (1, 2, 3, 4, 6, 8, 12 hours) and *k* and *n* coefficients of the Peppas kinetic equation. *In vitro* release study was carried out in accordance with the "Dissolution test for solid dosage forms" section from the European Pharmacopoeia (Eur. Ph.) under the following working conditions: apparatus: no. 2 (paddle); dissolution medium: phosphate buffer pH 6.8; dissolution medium volume: 900 mL; rotation speed: 50 rpm; drug assay: UV at 275 nm; dissolution time: 12 hours. Similar conditions were reported in the development of extended-release formulations with metoprolol tartrate in other studies.[9-11]

Kinetic release evaluation

Fitting the experimental data with different mathematical equations (first order, zero order, Korsmeyer-Peppas, Hixson-Crowell, and Baker-Lonsdale[3,13]) was performed to determine the release kinetics. When calculating the release kinetics, only a value higher than 80% was taken into account. Release kinetics is considered adequate if the correlation coefficient is close to 1[14,15] and index Akaike value is smallest.[16,17]

RESULTS AND DISCUSSION

To perform the work, a full factorial experimental design was used to study the influence of the ratio of granulation polymer (Eudragit NE 40D) and the ratio of Methocel K100 M on drug release and the type of release kinetics. The results obtained at *in vitro* release from metoprolol extended-release tablets prepared according to the experimental design are shown in Figure 1. For all the prepared formulations, the pharmacotechnical properties (friability, hardness, uniformity of weight) were within the limits according to Eur. Ph.

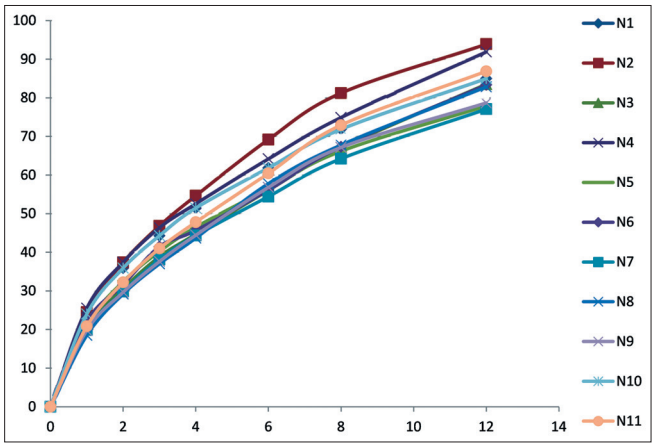

Figure 1: Drug dissolution profiles of formulations made according to the experimental design

To check the validity of the experimental design, the following statistical parameters were determined: R^2, Q^2, ANOVA.[12,18] The results obtained after fitting and calculation of the statistical parameters R^2 and Q^2 using data obtained in the experimental design are shown in Figure 2. The results of the ANOVA test (data not shown) were good for all responses (*P* for model was lower than 0.05 and *P* for residual was greater than 0.05 for all responses). According to available data (Q2, R2, ANOVA), it may be concluded that all the answers were satisfactory, fitted to the chosen model.

The results obtained at *in vitro* dissolution release of metoprolol extended-release formulation realized according to the experimental design are shown in Figure 1. Equation coefficients used for fitting the experimental data represent the influence of factors and the influence of interactions between factors on responses.[12,18] The influence of the formulation factors on the active substance release from the tablets is represented graphically in Figure 3 (as coefficient plot) and Figure 4 (as contour plot surface).

Eudragit NE was used in the formulation for the purpose of covering all or part of the metoprolol crystals during the granulation process, to reduce the release rate of metoprolol. Increasing the amount of Eudragit NE increases the thickness of the coating of metoprolol crystals, and hence the polymer film becomes stronger, less permeable, requiring a longer time so that water can enter inside the granules and determine the dissolution of metoprolol, leading to the decrease of the drug release. The second formulation factor serves for matrix formation that allows the drug release as the matrix erodes. Increasing the amount of Methocel has a negative influence on drug release, reducing the percentage of the drug dissolved for all times of determination. The analysis coefficient shows that the percentage of the drug released after one hour is influenced only by the ratio of Methocel (X_2); increasing the amount of Methocel K100 M reduces the rate of the drug released after one hour. The influence of polymer amount used in the

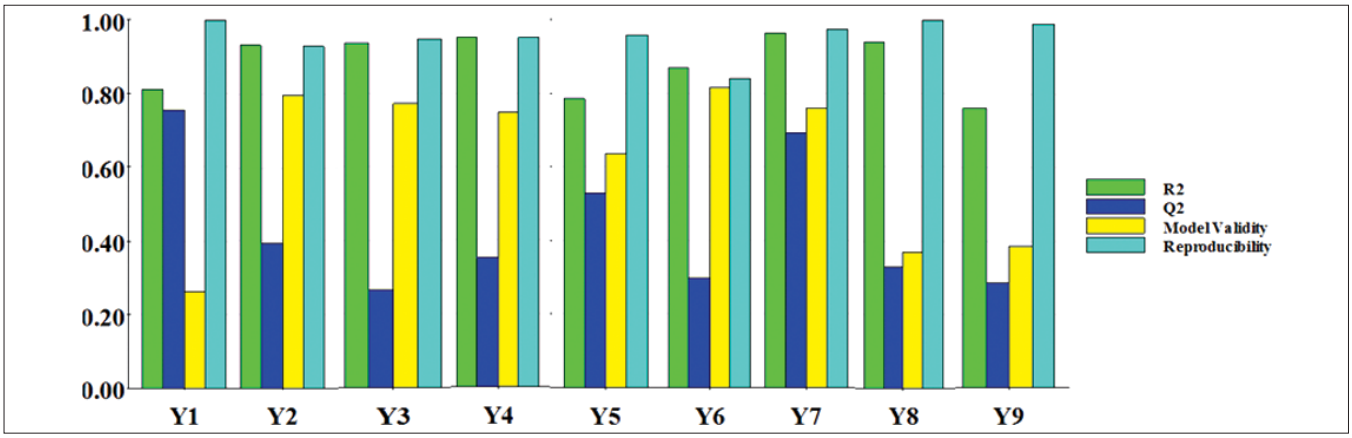

Figure 2: The fitting of the experimental data to the chosen model. Y_1: released at 1 hour, Y_2: released at 2 hours, Y_3: released at 4 hours, Y_4: released at 4 hours, Y_5: released at 6 hours, Y_6: released at 8 hours, Y_7: released at 12 hours, Y_8: *k* Peppas, Y_9: *n* Peppas

granulation process is insignificant. There are no interactions between the formulation factors for the sample taken at this determination time. But for all the other times studied (2, 3, 4, 6, 8, 12 hours), the percentage of the drug released is influenced both by the Eudragit ratio used as a binder (X_1), and the Methocel ratio (X_2); increasing the amount of both Eudragit NE 40D and Methocel K100 M reduces the percentage of the drug released. The intensity of the influence of the two formulation factors is approximately the same at two, three, and four hours, but the intensity of the X_1 factor is lower than that of the X_2 factor at six, eight, and 12 hours. The influence of the X_2 formulation factor on release has approximately the same intensity at all times studied, and the influence is linear in the experimental field. There are interactions between the formulation factors studied at two and four hours; concomitant increase of granulation polymer ratio (X_1) and Methocel ratio (X_2) do not reduce the percentage of the drug released at two and four hours. There are no interactions between the formulation factors

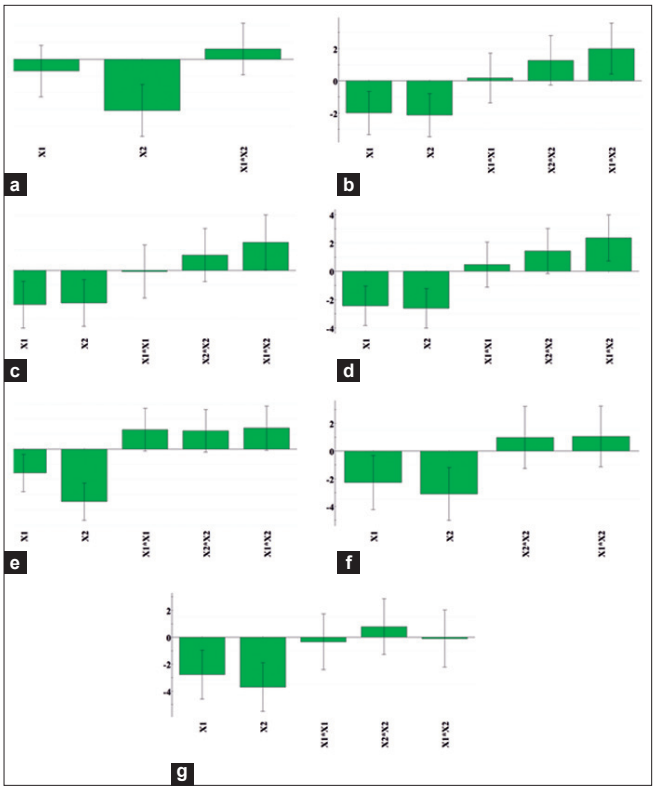

Figure 3: The influence of the formulation factors on the active substance release at different time intervals—coefficients plot presentation (a): 1 hour (Y_1), (b): 2 hours (Y_2), (c): 3 hours (Y_3), (d): 4 hours (Y_4), (e): 6 hours (Y_5), (f): 8 hours (Y_6), (g): 12 hours (Y_7), X_1: Eudragit ratio, X_2: Methocel ratio

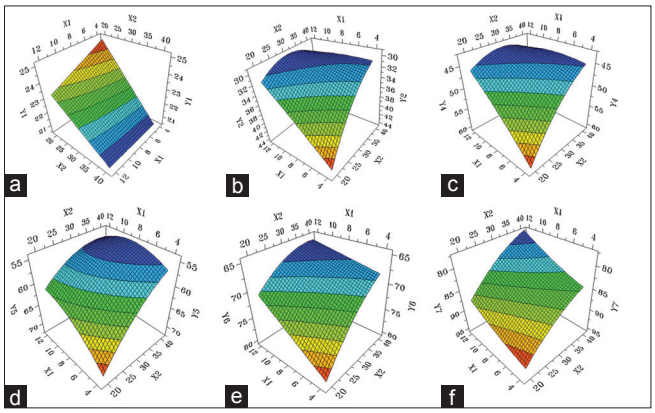

Figure 4: The influence of the formulation factors on the active substance release at different time intervals—contour plot surface presentation (a): 1 hour (Y_1), (b): 2 hours (Y_2), (c): 4 hours (Y_4), (d): 6 hours (Y_5), (e): 8 hours (Y_6), (g): 12 hours (Y_7). X_1: Eudragit ratio, X_2: Methocel ratio

Table 5: The results from fitting the data with different kinetic equations

		N1	N2	N3	N4	N5	N6	N7	N8	N9	N10	N11
Baker and lonsdale	*k*	0.0156	0.0162	0.0126	0.0176	0.0136	0.0122	0.0148	0.0118	0.0124	0.0131	0.0135
	r2	0.9872	0.9757	0.9692	0.9782	0.9750	0.9674	0.9667	0.9678	0.9880	0.9765	0.9747
	AIC	27.278	32.019	32.901	31.352	31.520	33.216	34.017	32.899	32.899	30.901	31.740
Peppas	*k*	25.734	24.540	20.613	26.155	22.290	20.032	22.251	19.787	22.995	22.124	22.043
	n	0.4867	0.5228	0.5635	0.5055	0.5368	0.5707	0.5566	0.5698	0.4983	0.5325	0.5408
	r2	0.9987	0.9991	0.9998	0.9998	0.9994	0.9990	0.9989	0.9989	0.9983	0.9989	0.9984
	AIC	15.501	14.010	3.961	6.146	11.330	14.277	15.461	14.609	16.295	14.412	17.087
Hixon and crowell	*k*	0.9332	0.9616	0.0425	0.0538	0.0446	0.0415	0.0474	0.0405	0.0420	0.0435	0.0446
	r2	0.0495	0.0508	0.9649	0.9526	0.9538	0.9674	0.9713	0.9645	0.9201	0.9462	0.9620
	AIC	37.045	34.705	33.683	35.942	35.148	33.219	33.136	33.473	37.242	35.769	34.152
Higuchi	*k*	25.100	25.613	23.234	26.423	23.887	22.8904	24.752	22.573	22.923	23.516	23.802
	r2	0.9984	0.9984	0.9947	0.9997	0.9975	0.9928	0.9948	0.9928	0.9983	0.9974	0.9961
	AIC	14.772	15.834	22.428	5.250	17.791	24.216	23.001	23.950	14.311	17.657	20.525
First order	*k*	0.1784	0.1828	0.1506	0.1949	0.1593	0.1466	0.1692	0.1429	0.1499	0.1549	0.1589
	r2	0.9724	0.9842	0.9842	0.9777	0.9784	0.9858	0.9867	0.9835	0.9637	0.9736	0.9863
	AIC	31.861	29.435	28.959	31.479	30.658	28.294	28.545	28.920	32.647	31.573	28.114
Zero order	k	8.7604	8.9959	8.2172	9.2577	8.4126	8.1036	8.7433	7.9916	8.0154	8.2770	8.3818
	r2	0.6136	0.7284	0.8132	0.6819	0.7622	0.8237	0.7995	0.8218	0.6559	0.7528	0.7683
	AIC	46.49192	45.690	43.224	46.464	44.362	42.884	44.250	42.703	45.117	44.290	44.372

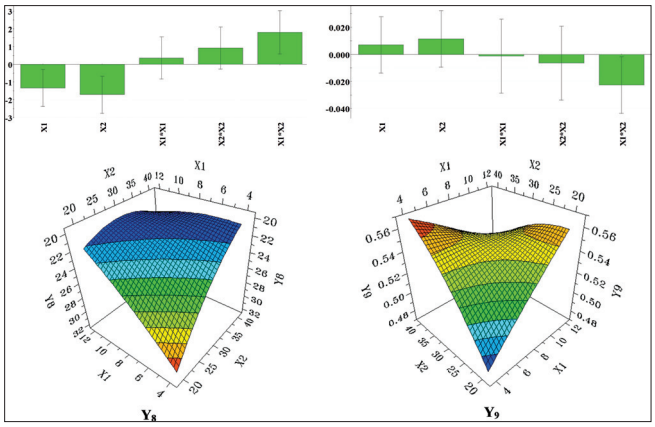

Figure 5: The influence of the formulation factors on kinetic release parameters. Y_8: *k* Peppas, Y_9: *n* Peppas; X_1: Eudragit ratio, X_2: Methocel ratio

studied at six, eight, and 12 hours. Similar results were obtained by other researchers. Nellore *et al*. studied the effect of HPMC amount on the release rate of metoprolol from tablets. They prepared tablets containing amounts of 10–40% HPMC. Increasing the percentage of HPMC from 10 to 40% significantly delayed the release of metoprolol tartrate from tablets prepared by direct compression. The effect was less obvious for tablets prepared using fluid bed granulation method.[2]

According to literature data, drug kinetic release from matrix tablets with HPMC is complex—swelling, diffusion, and erosion—and is based on the Korsmeyer-Peppas mathematical model.[19,20] The release from matrix tablets takes place in three steps. The first step is represented by the penetration of the dissolution medium inside the matrix (hydration), the second step, swelling and concurrent or subsequent matrix erosion, and the third step is the transport of the dissolved drug through the hydrated matrix or transport of the matrix fragments to the dissolution medium.[19] To study the kinetic release of metoprolol from prepared tablet formulation, six well-known kinetic release models were evaluated. The results obtained for the evaluation of kinetic release are presented in Table 5. The best fit of the *in vitro* release data was achieved for the Peppas model, for all formulations. Given that the best fit of kinetic release was obtained for the Peppas equation, the responses introduced in the experimental design were the two parameters of the Peppas equation (Y_8: *k* and Y_9: *n*). The coefficients of the equation used to fit the experimental data with the chosen model at kinetic release evaluation are presented as scaled and coefficient plot and as response plot surface in Figure 5. The analysis of the coefficients shows that the parameter *k* Peppas is influenced by both the formulation factors studied. The influence of the formulation factors on the parameter *k* Peppas is similar to the influence of the formulation factors on the *in vitro* release of metoprolol. The first formulation factor (Eudragit ratio: X_1) has a negative influence on the *k* Peppas parameter; increasing the percentage of the granulation polymer decreases the release rate of metoprolol and *k* Peppas value, respectively. Other researchers obtained similar results, which show that increased polymer concentrations (Kollidon SR) decrease the *k* Peppas release constant.[21] The second formulation factor (Methocel ratio: X_2) has a negative influence on the *k* parameter and on metoprolol release, respectively. Increasing HPMC K100 M concentration decreases the *k* Peppas value and also the metoprolol release. The intensity of the X_2 factor influence is slightly stronger compared to that of the X_1 factor. The intensity of the influence of the X_2 factor is not linear in the experimental field; it is intense between 20 and 33%, after which the intensity of the influence decreases. There is a strong interaction between the influence of the formulation factor X_1 and the influence of the formulation factor X_2 (X_1*X_2); the increase of both formulation factors does not lead to a decrease in *k*. There was no correlation found between the formulation factors studied and the *n* Peppas parameter, which means that the formulation factors studied do not influence the *n* Peppas parameter.

Using the results obtained from the experimental design, the following conclusions can be drawn: The percentage of the drug released during the 12 hours is influenced both by Eudragit ratio (X_1) and Methocel ratio (X_2); increasing the ratios of Eudragit and Methocel leads to the decrease of the percentage of the released drug. During the first hour, the Eudragit ratio (X_1) has no influence on drug release, but its influence increases at two hours and becomes maximum at four and six hours; all studied formulations showed a kinetic release that fitted best with the Peppas model, a model which shows that the release is influenced by metoprolol diffusion and the erosion of the matrix. No correlation was found between the studied formulation factors and the *n* Peppas parameter, suggesting that the studied formulation factors have no influence on this parameter.

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