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The Influence of Formulation Factors on the Kinetic Release of Metoprolol Tartrate from Prolong Release Coated Minitablets

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The aim of this work was to study the possibility to obtain an oral extended-release dosage forms with zero order kinetic release by coating minitablets (containing metoprolol tartrate) with insoluble methacrylate film coating (Eudragit NE 40D) in a fluidized bed system. To achieve this aim a full factorial experimental design with two factors and three levels was used in order to study de influence of the amount of polymer film formatting (Eudragit NE 40D) and the amount of pore generating excipient in polymeric insoluble film (low viscosity hydroxypropyl methylcellulose-Methocel E 15LV) on the in vitro drug release profile.

Keywords metoprolol tartrate; extended release minitablets; Eudragit NE; experimental design; optimization

INTRODUCTION

Metoprolol is a cardioselective beta-blocker and it is used in the management of hypertension, angina pectoris cardiac arrhythmias myocardial infarction, and heart failure (Sweetman, 2002). Metoprolol is absorbed in all parts of the intestine, after dosing with the conventional tablets, absorption is rapid and complete and has been classified in class I substances, according to the Bipharmaceutical Classification System (CDER, 2000; Klein & Dressman, 2006). The half-life of the metoprolol is stated to be 3–4 h. Metoprolol tartrate, with its incomplete oral bioavailability (due to extensive first-pass metabolism), short half-life, and multiple daily dosing, is appropriate for a formulation in a once-a-day extended-release dosage form. Therefore, metoprolol tartrate is the ideal candidate to a zero-order controlled release system because it is water-soluble and has a short half-life.

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Formulation of the reservoir-type extended release dosage forms consists of coating crystals, granules, pellets, and eventually tablets (or minitablets) with continue polymeric film, insoluble in all pH range, but permeable to water and drug solution (Kendall et al., 1991; Leucuta, 2001).

The first extended-release formulation with metoprolol was introduced on the market by Astra Zeneca in 1990 (Betok-Zok). This formulation consists on a tablet that rapidly disintegrates, releasing 0.5 mm diameter micropellets that contain metoprolol succinate. Each of the pellets is designated to act as a diffusion cell that delivers the drug at a relatively constant rate, essentially relatively independent of physiological variation within the GI tract (Efentakis et al., 2000).

The ideal release of drug from the oral extended release dosage form is the zero order profile. This is the situation in which the drug is released from the dosage form at the same slow rate throughout the entire release period (Pather et al., 1998).

The aim of this work was to study the possibility of obtaining an extended-release oral solid dosage form with zero order kinetic release by coating minitablets, containing metoprolol tartrate, with insoluble methacrylate film coating (Eudragit NE 40D) in a fluidized bed system (Aeromatic Strea 1).

MATERIAL AND METHODS

Materials

Metoprolol tartrate (Sun Pharmaceutical, India); dicalcium phosphate dihydrate (Rhodia Inc., SUA); microcrystalline cellulose type PH 102 (JRS Pharma, Germany); co-processed excipient-CELLLACTOSE 80 (Meggle, Germany); polyvinylpyrrolidone type K_{25} (BASF, Germany); talcum (S&D Chemicals, UK); magnesium stearate (Union Derivan, Spain); stearic acid (Merck, Germany); Eudragit NE 40D (Degussa, Germany); hydroxypropyl methylcellulose–Methocel type E 15LV-HPMC (Colorcon); titan dioxide (S&D Chemicals); Simeticone (Colorcon).

Apparatus

Tablet press EK-0 (Korsch, Germany), laboratory kneader LK5 (Erweka, Germany), laboratory wet granulator FGS (Erweka, Germany) planetary mixer PRS (Erweka, Germany), laboratory fluidized bed system Strea 1 (Aeromatic, Switzerland), UltraTurax (Janke and Kunkel, Germany), dissolution apparatus PT-DT7 (PharmaTest, Germany), spectrophotometer UV-Vis V530 (Jasco, Japan).

Experimental Design

In order to study the formulation factors that influence the drug release especially for drug release modulation, a full experimental design with two factors and three levels was used. The formulation factors (Table 1) were the amount of polymeric film used for coating (Eudragit NE 40D) and the amount of pore generating excipient in polymeric insoluble film (low viscosity hydroxypropyl methylcellulose-Methocel E 15LV). The matrix of the experimental design is presented in Table 2. The responses were the percent of drug release at different time intervals and the zero order kinetic release constant (Table 3).

Software

The experimental design, the calculation of the coefficients and of the statistical parameters and the evaluation of the quality of the fit were performed with Modde for Windows (Version 6.0, Umetrics AB, Umea, Sweden) (MODDE 6, Umetrics Academy, 2001).

TABLE 1
Independent Variables

		Level		
Formulation Variables		−1	0	1
Percent of Eudragit NE	X_1	4%	8%	12%
Percent of HPMC	X_2	2%	6%	10%

TABLE 2
The Matrix of the Experimental Design

Exp No	Run Order	X_1	X_2
N1	11	4	2
N2	8	8	2
N3	9	12	2
N4	4	4	6
N5	10	8	6
N6	3	12	6
N7	6	4	10
N8	7	8	10
N9	5	12	10
N10	2	8	6

X_1–Percent of Eudragit NE; X_2–Percent of HPMC.

TABLE 3
Dependent Variables (Responses)

Reponses	Symbol
% of the metoprolol released at 1 h	Y_1
% of the metoprolol released at 2 h	Y_2
% of the metoprolol released at 4 h	Y_3
% of the metoprolol released at 8 h	Y_4
% of the metoprolol released at 12 h	Y_5
% of the metoprolol released at 16 h	Y_6
% of the metoprolol released at 20 h	Y_7
% of the metoprolol released at 24 h	Y_8
% of the metoprolol released at 30 h	Y_9
% of the metoprolol released at 36 h	Y_{10}
k–kinetic release constant (zero order)	Y_{11}

MINITABLETS PREPARATION

The minitablets were obtained via wet granulation using a Korsch EK 0 eccentric press equipped with die and punches of 5 mm. The machine was regulated to obtain minitablets of 75 mg weight and hardness of minimum 6 kg force. The composition (both qualitative and quantitative) of the minitablets is presented in Table 4. The granules with metoprolol tartrate were obtained via wet granulation of the powders blend are presented in Table 5, in a laboratory kneader Erweka LK5, with polyvinylpyrrolidone

TABLE 4
Minitablets Preparation Formulas (Qualitative and Quantitative)

	mg/Minitablet	g/Batch	%
Granules with metoprolol tartrate	50	700	66.7
CELLLACTOSE 80	22.75	318.5	30.3
Talcum	0.75	10.5	1
Magnesium stearate	0.75	10.5	1
Stearic acid	0.75	10.5	1

TABLE 5
Wet Granulating Formula

	g	%
Metoprolol tartrate	350	50.00
Dibasic calcium phosphate	135	19.29
Microcrystalline cellulose	200	28.57
Povidone K25*	15	2.14

*aqueous solution 20%.

K_{25} aqueous solution. After sieving in an Erweka FGS wet granulator (sieves 1.00 mm) the granules were dried in an oven for 24 h. In order to obtain a sufficient amount of cores for all minitablets coating studies, two batches of 1050 g were prepared.

Characterization of Tablets

The tablets were tested for hardness, friability, and mass uniformity. Hardness of tablets was determined by using the Monsanto hardness tester. Friability and mass uniformity were determined by using methods described in PhEur 5 (European Pharmacopoeia, 2005).

Coating Minitablets

The minitablets were coated with an insoluble polymeric film but permeable (Eugragit NE 40D), in a fluidized bed coating device (Strea 1, Aeromatic Filder). The amount of film formatting polymer (Eudragit NE 40D) and the amount of pores generating in insoluble film (HPMC) was different from an experiment to other according to the experimental design matrix. The technological parameters during the coating process are shown in Table 6.

Dissolution Studies

The dissolution studies were performed with a PharmaTest PT-DT7, in phosphate buffer at pH 6.8 using the basket method at a 100 rpm rotation speed (PhEur 5 apparatus 2). Four minitablets (each minitablet contains 25 mg of metoprolol tartrate) were put into a vessel with 1000 mL dissolution media. At specific time intervals 5 mL solutions were withdrawn, immediately filtered through a 0.45 μm filter and the drug concentration was assayed with the UV spectrophotometer (Jasco V 530, Japan), using 273 nm wavelength. The initial volume of the vessel was maintained by adding 5 mL of fresh medium after each sampling. For each formulation, the dissolution studies were performed thrice.

To evaluate the dissolution profiles, several release models (Table 7) were tested such as zero order (Macheras et al., 1995; Wagner, 1969), Korsmeyer-Peppas (Korsmeyer et al., 1983; Peppas, 1985), Hixson-Crowell (Hixson & Crowell, 1931) and Baker-Lonsdale (Baker & Lonsdale, 1974). The mathematical models, shown in Table 7, were fitted to individual dissolution data with the regression module of Kinetica 4.4 for Windows. To calculate kinetic release only a value grater than 80% was taken into consideration.

TABLE 6
Process Parameters During Coating

Parameters	Value
Charge load (g)	180
Nozzle bore (mm)	0,8
Atomizing pressure (atm)	2,6–2,8
Spray rate (g/min)	6
Inlet air temperature (°C)	36–42
Outlet air temperature (°C)	28–34
Fan air (m^3/min)	7–9
Preheating time (min)	1
Final drying at 40°C (min)	10

TABLE 7
Release Models Tested

Zero order	$Q_t = Q_0 + K_0 t$
Korsmeyer- Peppas	$Q_t / Q_\infty = K_k t^n$
Hixson-Crowell	$Q_0^{1/3} - Q_t^{1/3} = K_s t$
Baker-Lonsdale	$(3/2)[1 - (1 - (Q_t / Q_\infty)^{2/3}] - (Q_t/Q_\infty) = Kt$

RESULTS AND DISCUSSIONS

Results Obtained from the Minitablets Preparation

The minitablets used as cores in coating process, need to have suitable physico-chemical properties regarding the compaction, impaction, and attrition strengths in order to avoid ruptures during the fluid bed coating process (Cole et al., 1995). A lower value for the friability of the minitablets and a high value of their hardness is the prerequisite to a successful processing. Due to the fact that metoprolol tartrate has poor compaction properties, the minitablets were obtained in two steps via wet granulation. In order to improve tableting properties of metoprolol granules, during the second step, a co-processed direct compression excipient (CELLLACTOSE 80) was added in an amount of approximately 50%. The results obtained in the preparation of minitablets are presented in Table 8.

The results presented in Table 8 show that minitablets have a low mass variability, have good hardness, and have a very low friability. More than that, there are no significant differences among the properties obtained in the two batches of minitablets. These minitablets have suitable pharmaco-technical properties for coating in fluidized bed device.

Experimental Design Analysis. Goodness of Fit

The matrix of the results is shown in Table 9. The dissolution profiles obtained from coated minitablets prepared according to the experimental design are shown in Figure 1.

TABLE 8
Minitablets Properties

	Mass Uniformity		Hardness
	Mean *SD*	Friability	Mean *SD*
Batch #1	75.10 mg ± 2.94	0.000%	7.4 kg ± 1.03
Batch #2	76.02 mg ± 2.62	0.044%	6.7 kg ± 0.62

TABLE 9
The Matrix of the Responses

Exp No	Y_1	Y_2	Y_3	Y_4	Y_5	Y_6	Y_7	Y_8	Y_9	Y_{10}	Y_{11}
N1	11	22.23	42.13	76.95	87.69	95.23	98.12	101.1	102.18	100.94	8.260
N2	1.81	0.43	2.08	1.67	2.26	2.12	2.22	3.66	18.68	33.64	0.544
N3	1.52	0.48	1.98	2.02	2.46	3.11	2.93	3.44	2.31	8.89	0.174
N4	1.77	1.28	5.5	21.7	43.06	50.24	63.45	75.38	84.58	90.8	3.044
N5	1.23	0.09	0.46	0.26	0.67	1.11	1.21	2.67	20.47	32.33	0.519
N6	1.34	1.06	0.64	1.03	1.38	2.23	3.34	3.59	9.21	23.52	0.367
N7	4.35	8.93	20	41.5	66.29	79.7	88.2	95.52	97.1	98.35	4.824
N8	1.34	0.5	1.05	0.42	7.85	27.34	40.56	56.1	66.74	74.54	2.019
N9	0.31	1.62	1.08	0.43	2.15	8.78	16.09	22.68	40.52	52.14	1.131
N10	0.3	0.66	2.18	2.44	3.81	14.56	24.82	34.67	49.44	59.6	1.440

Y_1-% of the metoprolol released at 1 h; Y_2-% of the metoprolol released at 2 h, Y_3-% of the metoprolol released at 4 h, Y_4-% of the metoprolol released at 8 h, Y_5-% of the metoprolol released at 12 h, Y_6-% of the metoprolol released at 16 h, Y_7-% of the metoprolol released at 20 h, Y_8-% of the metoprolol released at 24 h, Y_9-% of the metoprolol released at 30 h, Y_{10}-% of the metoprolol released at 36 h, Y_{11}–kinetic release constant (zero order).

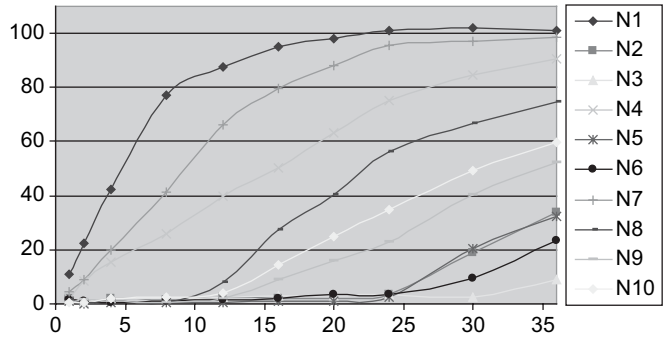

FIGURE 1. The percent of the metoprolol tartrate released from the experimental formulations (N1–N10 see Table 2) at different dissolution time points.

In order to fit the experimental data with chosen experimental design and to the calculation of the statistical parameters, the statistical module from Modde 6 software was used. To check the validity of the experimental design the following statistical parameters were determined: R^2, Q^2, and ANOVA test. R^2 represents the fraction of variation of the response explained by the model and Q^2 represents the fraction of variation of the response that can be predicted by the model. Both R^2 and Q^2 values are numbers, usually between 0 and 1. Values close to 1 for both R^2 and Q^2 indicate a very good model with excellent predictive power. R^2 and Q^2 provide the best summary of fitting the model. R^2 represents overestimated and Q^2 underestimated measures respectively of the goodness of fit of the model (Erikkson et al., 2000).

The results obtained after the fitting and the statistical parameters calculation using data obtained from the experimental design, are shown in Figure 2.

The results fit very well for Y_6–Y_{11} responses and are satisfactory for Y_1–Y_5 responses.

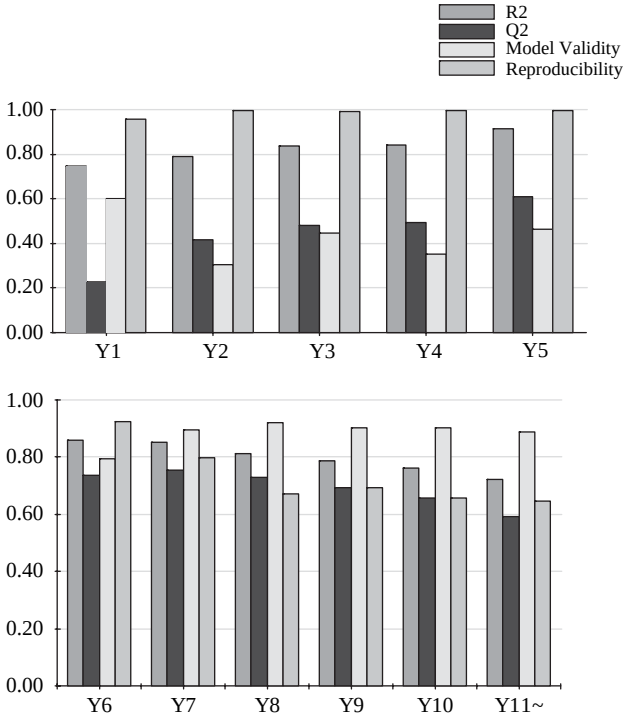

FIGURE 2. The fitting of the experimental data with the chosen model. Y_1-% of the metoprolol released at 1 h; Y_2-% of the metoprolol released at 2 h, Y_3-% of the metoprolol released at 4 h, Y_4-% of the metoprolol released at 8 h, Y_5-% of the metoprolol released at 12 h, Y_6-% of the metoprolol released at 16 h, Y_7-% of the metoprolol released at 20 h, Y_8-% of the metoprolol released at 24 h, Y_9-% of the metoprolol released at 30 h, Y_{10}-% of the metoprolol released at 36 h, Y_{11}–kinetic constant (zero order).

ANOVA test (analysis of variance) shows if the variance of the results is determined by modifications of the formulation factors or represents a variance determined by experimental errors (MODDE 6, Umetrics Academy, 2001). The results of

ANOVA test shown that the experimental data obtained for Y_2–Y_{11} responses were good (p for model was lower than 0.05 and p for residual was greater than 0.05) for all responses.

EXPERIMENTAL DESIGN ANALYSIS. FORMULATION FACTOR ANALYSIS

Eudragit NE 40D is an aqueous dispersion of a neutral copolymer based on ethyl acrylate and methyl methacrylate widely used to obtain reservoir type extended release formulation. Compared to Eudragit RS and RL is highly flexibility polymer that requires no plasticizer. It is insoluble but swellable in water and has low permeability (Eudragit NE 40D Technical Specification, 2005). To increase the film permeability an easy soluble polymer (low viscosity HPMC Methocel E 15 LV) was used as pores generating. A two-factor, three-level full experimental design was applied to construct a second-order polynomial model describing the effect of the formulation factors on the characteristics of the product.

The amount of the polymeric film formatting, Eudragit NE 40D, has the most important effect on the metoprolol release at all dissolution time points.

The increase of the amount of polymer reduced the % of the metoprolol tartrate released at all dissolution time points (Figure 3). The effect has approximated the same intensity at all dissolution time points (Figure 3). The effect of the percent of Eudragit NE 40D is nonlinear at the dissolution points between 1–12 h, and presents a maximum at 9–10% (Figure 4a, b). The effect of the percent of Eudragit NE 40D is approximately linear at dissolution point between 16–36 h (Figure 4c, d).

The influence of the amount of HPMC on the drug release is less significant than the amount of Eudragit NE and is different function of the dissolution time points.

In the first 8 h the increase of the percent of HPMC reduced the metoprolol % release (Figure 3a, b and Figure 4a, b), but after 12 h the percent of HPMC slightly increased the % of metoprolol release (Figure 3a, b).

Dissolution Release Analysis

The results obtained for kinetic release characterization are shown in Table 10. The best fitting for the drug release was obtained with the zero-order kinetic. The ideal value of the zero-order kinetic release constant to delivery metoprolol for a period of 30 h is 3.334. Ideal value of the zero-order kinetic release constant was used as a response of the experimental design, in order to determine independent variables.

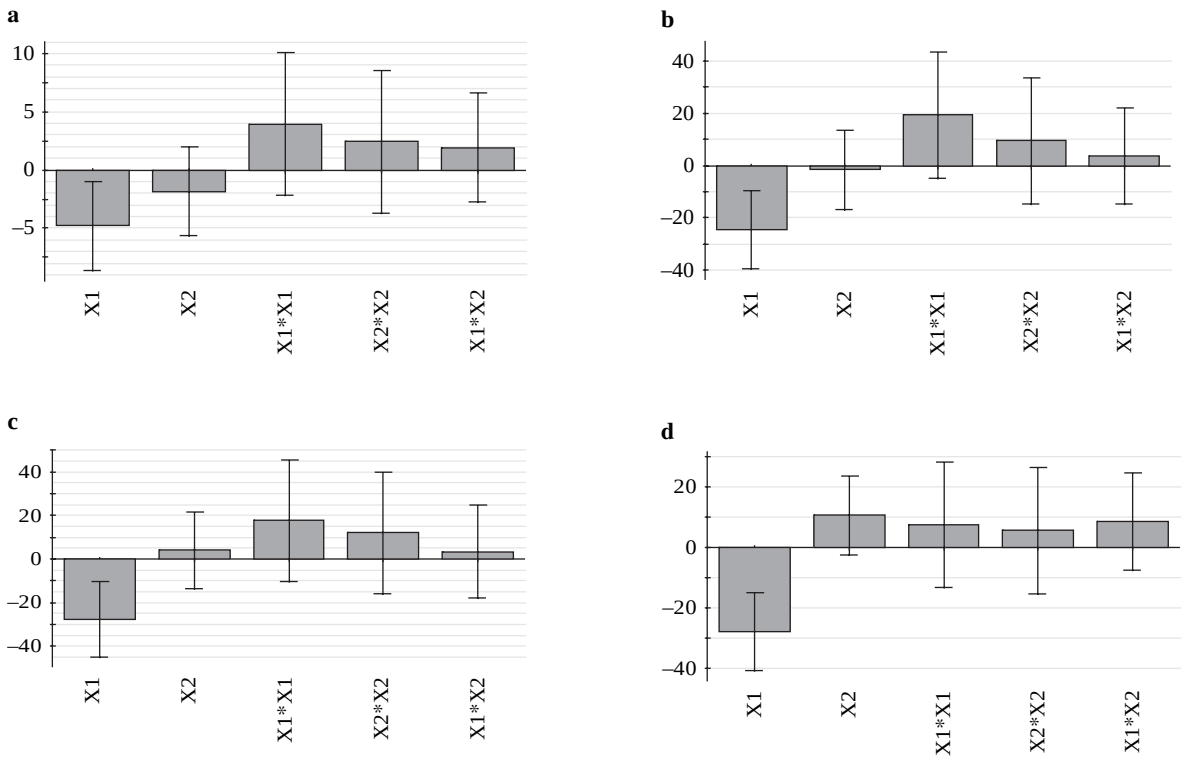

FIGURE 3. The influence of the formulation factors on the metoprolol release at different time intervals. (a) – Y_2-% of the metoprolol released at 2h; (b) – % of the metoprolol released at 12 h; (c) – Y_6-% of the metoprolol released at 16 h; (d) – Y_{10}-% of the metoprolol released at 36 h. X_1-Percent of Eudragit NE; X_2-Percent of HPMC).

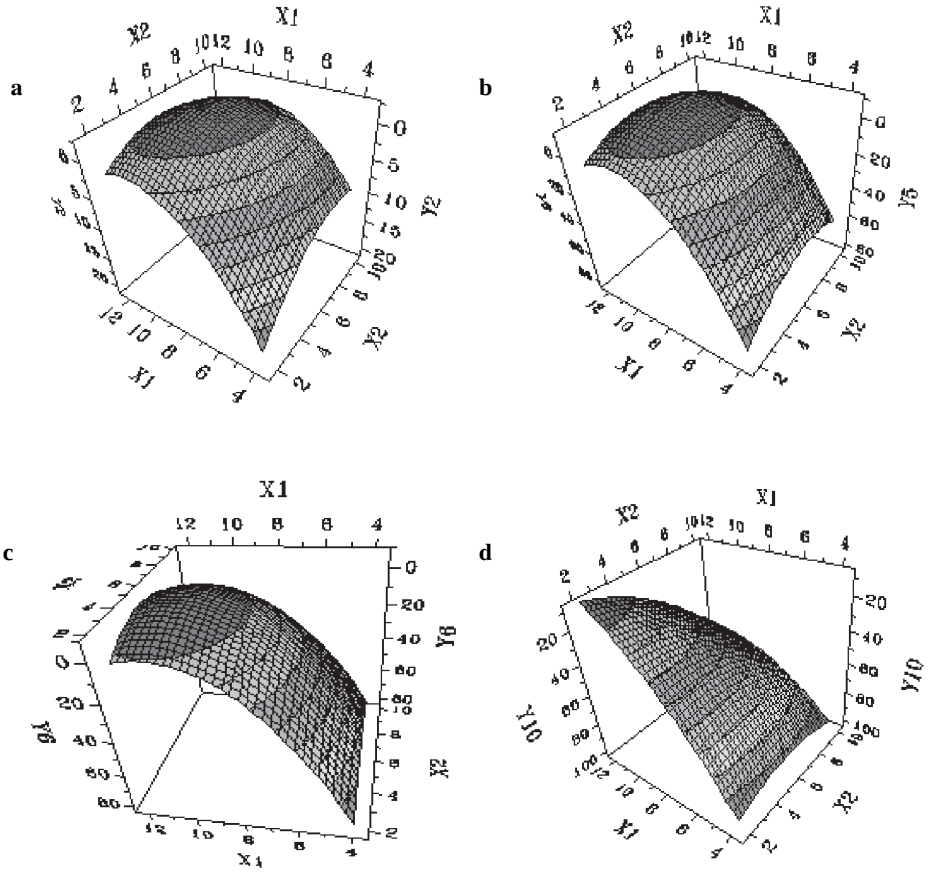

FIGURE 4. The influence of the formulation factors on the metoprolol release at different time intervals. (a) – Y_2-% of metoprolol released at 2 h; (b) – % of the metoprolol released at 12 h; (c) – Y_6-% of the metoprolol released at 16 h; (d) – Y_{10}-% of the metoprolol released at 36 h. X_1-Percent of Eudragit NE; X_2-percent of HPMC).

TABLE 10
The Results Obtained at the Kinetic Release Characterization

		N1	N2	N3	N4	N5	N6	N7	N8	N9	N10	Ideal
Zero order	K	8.260	0.544	0.174	3.044	0.519	0.367	4.824	2.019	1.131	1.440	3.333
	r2	0.9570	0.7637	0.7480	0.9936	0.7463	0.7734	0.9890	0.9549	0.9084	0.9444	0.9999
Peppas	K	14.92560	0.00010	0.24340	4.56500	0.00008	0.00001	6.70890	0.52970	0.00001	0.13910	3.33220
	N	0.735	2.796	0.897	0.869	4.092	3.411	0.879	1.407	6.133	1.706	1.000
	r2	0.9872	0.2340	0.7490	0.9978	0.2220	0.2340	0.9926	0.9762	0.1584	0.9911	1.0000
Hixon and	K	0.0439	0.0019	0.0006	0.0141	0.0018	0.0013	0.0237	0.0082	0.0041	0.0054	0.0157
Crowell	r2	0.9966	0.7517	0.7469	0.9948	0.7349	0.7658	0.9916	0.9306	0.8882	0.9230	0.9799
Baker and	K	0.01350	0.00010	0.00001	0.00400	0.00010	0.00005	0.00710	0.00170	0.00050	0.00080	0.00470
Lonsdale	r2	0.9106	0.5922	0.7122	0.9129	0.5677	0.6070	0.8960	0.7947	0.7412	0.7765	0.8836

Optimum Formula Determination

Using the optimization module from Modde 6.0 software and value of 3.334 as the ideal value for the response Y_{11} led to the theoretical determination of the optimum (Table 11). The experimental value obtained for the optimum formula was close to the theoretical results predicted by the experimental design (Table 12).

TABLE 11
The Optimum Formula

Formulation Variables	Symbol	Level
Procent of Eudragit NE	X_1	4.8
Procent of HPMC	X_2	6

TABLE 12
The Optimum Formula–Results

	Y1	Y2	Y3	Y4	Y5	Y6	Y7	Y8	Y9
Theoretical	3.6038	7.1938	14.3763	23.5017	38.1116	55.2260	65.5414	73.2267	85.7184
Obtained	4.17	9.28	16.53	28.913	42.08	56.45	68.455	78.38	87.58

The results obtained in this work show that it is relatively easy to obtain prolonged release formulation with metoprolol that has the desired in vitro dissolution profile release if a statistical approach is used in formulation studies.

Until now there were performed many studies for in vitro–in vivo correlation on immediate release and controlled release oral dosage forms (Eddington et al., 1998; Emami, 2006; Mahayni et al., 2000; Mauger & Chinchilli, 1997; Nellore et al., 1998; Sirisuth & Eddington, 2002; Uppoor, 2001) and some of them were on metoprolol extended release dosage forms (26–26). These studies showed a good in vitro–in vivo correlation for metoprolol from extended release formulations if dissolution studies are performed in phosphate buffer at pH 6.8 and not in HCl 0.1 N solution at pH 1.2 (Sirisuth & Eddington, 2002; Eddington et al., 1998).

This means that it is relatively easy to formulate and to obtain oral dosage forms with desired plasma profile by combining in vitro–in vivo correlation studies, with a statistical (experimental design) formulation approach and use kinetic release constant as a dependent variable of the experimental design.

CONCLUSIONS

The formulation factors that influence the in vitro kinetic release of metoprolol tartrate from extended release minitablets was studied by using full experimental design with two factors and three levels.

The amount of the film formatting polymer (Eudragit NE 40D) has the most important influence on the percent of drug release at all dissolution time points. The results obtained on dissolution profiles evaluated with four kinetic release models show that best fitting was obtained with the zero order kinetic release model.

The theoretical results predicted with experimental design were very close to the experimental results obtained by the optimum formula calculated with the optimization module from Modde 6.0 (software used for the construction and analysis of the experimental design).

In conclusion, by using the kinetic release constant of drug as a dependent variable in the experimental design, after the realization and validation of the experimental design, the level of the formulation variables can be easily determinate in order to obtain the desired kinetic release. This work illustrates the simplicity of modulating of the desired kinetic release from the extend release dosage form by using experimental design to study the influence of the formulation factors on the in vitro dissolution behavior and the kinetic release constant as a response. This means that statistical formulation approach in combination with in vitro–in vivo correlation studies make it easy to formulate and to obtain oral extended release dosage forms with desired plasma profile.

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