

EXPERIMENTAL DESIGN FOR THE SCREENING OF THREE TYPES OF COATING POLYMERS FOR METOPROLOL MINITABLETS WITH PULSATILE RELEASE

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Abstract

The aim of this work was to prepare pulsatile release metoprolol tablets coated with three different polymers in order to determine which polymer is best suited to this type of chronotherapeutical formulations for further experiments. An experimental design with three factors and three levels was used for this purpose, observing the influence of the formulation variables on the drug release profiles. The studied factors were: the polymer type (Eudragit NE, Eudragit RS and Surelease), the polymer percent and the sodium starch glycolate percent (swelling agent) used in the formulation. The tablets were analyzed regarding the *in vitro* dissolution behaviour and the obtained release profile. The results showed that higher concentrations of swelling agents increased the drug release, while higher concentrations of polymer decreased it. The best suited polymer was Eudragit RS, because it allows the variation of another formulation factor, respectively the film plasticizer percent.

Rezumat

Obiectivul acestei lucrări a fost prepararea de comprimate cu metoprolol cu eliberare pulsatorie, acoperite cu trei tipuri de polimeri, pentru a determina polimerul cel mai potrivit acestui tip de formulare cronofarmaceutică, pentru a fi utilizat în experimente ulterioare. În acest scop a fost dezvoltat un plan experimental cu trei factori și trei nivele, observându-se influența variabilelor de formulare asupra profilului de eliberare a substanței medicamentoase. Factorii studiați au fost: tipul polimerului (Eudragit NE, Eudragit RS și Surelease), procentul de polimer și procentul de amidon glicolat de sodiu (agent de umflare) din formulare. Comprimatele au fost caracterizate din punctul de vedere al dizolvării *in vitro* și al profilului de cedare obținut. Rezultatele au arătat că o creștere a cantității de agent de umflare duce la eliberarea unei cantități mai mari de substanță medicamentoasă, în timp ce o creștere a cantității de polimer duce la eliberarea unei cantități mai mici. Cel mai potrivit polimer este Eudragit RS, deoarece permite și modificarea unui alt factor în formulare, reprezentat de procentul de plastifiant din film.

Keywords: pulsatile release, metoprolol, Eudragit RS, Eudragit NE, experimental design, Surelease.

Introduction

In the present paper we have studied the influence of three different coating polymers on the release profile of a model drug, metoprolol, a beta-blocker used in the treatment of hypertension [3]. We evaluated which of the three polymers is best suited for an appropriate pulsatile release for an efficient chronotherapeutical treatment of hypertension. We also evaluated the drug concentration during the day in order to better control blood pressure. For a person who is awake during the daytime and asleep during the night-time, blood pressure increases in the early morning upon awakening, reaches a plateau at the highest values of the day during work or physical activity, and declines to its lowest value around midnight. It is thought that clinically effective plasma drug concentrations in the early morning would maximize an anti-hypertensive drug's effect on blood pressure. Paradoxically, the morning effort for taking this drug might induce the morning surge in blood pressure that the drug is designed to prevent. Thus, a formulation with a lag time before drug release might achieve the desired drug concentration profiles. [2, 5, 6, 7, 8]

Minitablets covered with polymeric film were manufactured, made up of a drug-loaded swelling core and a permeable film through which water can penetrate, causing the core to swell, breaking the polymeric film and releasing the drug.

An experimental design with three factors and three levels was used in order to observe the influence of the formulation variables on the tablets' release profiles [4, 11].

Materials and Methods

Materials

Metoprolol tartrate (Microsin, Romania); monohydrate lactose 800 M (HMS, Holland); microcrystalline cellulose - PH 102 (JRS Pharma, Germany); sodium starch glycolate (JRS Pharma, Germany); fumed silica - Aerosil (BASF, Germany); magnesium stearate (Merck, Germany); polyvinylpyrrolidone K25 (Merck, Germany); talcum (S&D Chemicals, UK); Eudragit RS 30D (Rohm Pharma, Germany); Eudragit NE 40D (Rohm Pharma, Germany); Surelease (Colorcon, UK); triethylcitrate (Merck, Germany); Simeticone (Colorcon, UK).

Experimental Design

A fractional Box Behnken experimental design with three factors and three levels was used to perform the study.

Table I
Independent variables

Formulation Variables	Symbol	Level		
		-1	0	+1
Polymer type	X ₁	Eudragit NE	Eudragit SR	Surelease
Sodium starch glycolate concentration	X ₂	5	-	20
Polymer concentration	X ₃	5 (6)	-	25(30)

Table II
Responses studied

No.	Response	Symbol
1	% released at 0.5h	Y ₁
2	% released at 1.0h	Y ₂
3	% released at 1.5h	Y ₃
4	% released at 2.0h	Y ₄
5	% released at 2.5h	Y ₅
6	% released at 3.0h	Y ₆
7	% released at 3.5h	Y ₇
8	% released at 4.0h	Y ₈
9	% released at 4.5h	Y ₉
10	% released at 5.0h	Y ₁₀
11	% released at 5.5h	Y ₁₁
12	% released at 6.0h	Y ₁₂
13	% released at 6.5h	Y ₁₃
14	% released at 7.0h	Y ₁₄

Table III
The Experimental Design Matrix

Exp. Name	Run Order	X ₁	X ₂	X ₃
E1	1	Eudragit NE	20	25
E2	2	Eudragit NE	20	5
E3	3	Eudragit NE	5	5
E4	4	Eudragit RS	20	25
E5	5	Eudragit RS	20	5
E6	6	Eudragit RS	5	5
E7	7	Surelease	20	30
E8	8	Surelease	20	6
E9	9	Surelease	5	6
E10	10	Eudragit RS	20	5
E11	11	Eudragit RS	11	5

X₁ –Polymer type; X₂ – Sodium starch glycolate percent; X₃ – Polymer percent

Eleven experimental determinations were performed for a factorial experimental design (2^{3-3}) with three factors and three levels. The independent variables (formulation factors) and the variation levels are presented in Table I. The responses studied are presented in Table II. The experiments were performed in the run order specified in the experimental design matrix in Table III. The experimental design, the coefficient calculation, the statistic parameter calculation and the evaluation of the quality of the fit were performed using the Modde 6.0 software (Umetrics, Sweden).

Tablet preparation

The materials – metoprolol 25 mg/tablet (33.34%), sodium starch glycolate 5% or 20%, and monohydrate lactose 54.33% or 8.99%, respectively, underwent a granulation step using a 10% polyvinylpyrrolidone solution, in a Strea 1 fluid bed granulator (Aeromatic, Switzerland).

After the granulation process and after the addition of 3% or 33% microcrystalline cellulose, 1% magnesium stearate and 1% fumed silica, the tablets were obtained by compression using an eccentric press (Korsch EK 0, Germany) equipped with a set of biconvex punches of 5 mm. The machine was set to obtain 75 mg tablets, with a mechanical resistance of 5-9 kg. The tablets were then coated in a Strea 1 fluid bed granulator (Aeromatic, Switzerland) equipped with a 0.8 mm pulverization duze. The coating solutions were different aqueous solutions of Eudragit NE (5%, 25%), Eudragit RS (5%, 25%) (adding 11% triethylcitrate as plasticizer), or Surelease (6%, 30%).

In vitro release studies

The *in vitro* dissolution tests were performed in a PharmaTest PT-DT7 device, which was equipped with the USP no. 1 apparatus (with paddles) employed at 50 rpm rotation speed. The dissolution media used was 500 mL phosphate buffer (pH=6.5) at 37°C. Four tablets each containing 25 mg metoprolol (100 mg total) were immersed in the dissolution media. Two samples were collected at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5 and 7 hours. Each 5 mL sample were immediately filtered through a 0.45 μ m filter and replaced with fresh media to maintain a constant volume during the experiment. The sample solutions were analyzed at 275 nm by UV spectrophotometry, and a mean value of the results of the two samples was calculated for each dissolution time.

Results and Discussion

Experimental design analysis. Quality of the fit.

The statistical module from the Modde 6 software was used in order to fit the experimental data with the chosen experimental design and to calculate the statistical parameters, with the Partial Least Squares method. To check the validity of the experimental design the following statistical parameters were calculated: R^2 , Q^2 and the ANOVA test. R^2 represents the variation fraction of the response explained by the model and Q^2 represents the variation fraction of the response that can be predicted by the model. Values close to 1 for both R^2 and Q^2 indicate a very good model with an excellent predictive potential [1, 10]. The values of R^2 , Q^2 and the ANOVA test were good, indicating a good quality of the fit.

The study of *in vitro* release of metoprolol

The matrix of results is shown in table IV. The results indicate that the percent of metoprolol released depends on the formulation factors studied in the experimental design (Table I). The release profiles of metoprolol from the formulations are shown in figure 1.

Table IV
Matrix of responses

Exp. Name	E1	E2	E3	E4	E5	E6	E7	E8	E9	E10	E11
Y ₁	4.03	2.87	0.84	4.46	57.55	0.89	2.4	82.52	11.27	49.2	5.33
Y ₂	1.01	1.15	0.36	3.8	98.28	2.44	0.54	98.9	57.82	55.42	8.08
Y ₃	0.16	1.88	0.02	4.29	100.53	3.57	1.89	100.28	78.58	80.85	17.41
Y ₄	0.44	2.83	0.23	4.68	100.63	4.51	0.59	105.05	84.27	100.7	41.38
Y ₅	0.81	28.54	0.77	5.01	101.39	5.25	0.42	100.28	85.94	100.87	51.86
Y ₆	1.1	54.37	0.67	5.06	101.39	5.94	0.36	100.51	88.07	103.44	61.05
Y ₇	0.64	69.5	0.77	5.41	102.13	6.32	0.6	100.93	87.95	103.43	70.02
Y ₈	0.91	86.74	1.62	5.58	101.95	6.62	0.66	101.66	88.23	102.28	73.59
Y ₉	0.7	92.29	1.44	5.46	102.08	6.9	0.59	100.7	89.11	101.47	80.3
Y ₁₀	0.51	102.15	1.25	7.21	102.02	7.29	0.8	100.38	88.21	102.36	85.22
Y ₁₁	0.99	102.55	1.82	5.88	101.27	7.34	1.73	99.77	88.52	101.78	87.18
Y ₁₂	1.29	103.28	3.32	5.91	100.24	7.5	1.48	99.45	87.99	101.75	88.94
Y ₁₃	0.65	102.81	3.77	5.75	99.54	7.62	1.09	96.01	87.16	99.64	91.5
Y ₁₄	0.5	103.47	2.25	5.91	97.9	7.72	0.79	96.29	86.26	98.5	92.41

Y₁ - Percent of metoprolol released after 0.5h; Y₂ - Percent of metoprolol released after 1.0h; Y₃ - Percent of metoprolol released after 1.5h; Y₄ - Percent of metoprolol released after 2.0h; Y₅ - Percent of metoprolol released after 2.5h; Y₆ - Percent of metoprolol released after 3.0h; Y₇ - Percent of metoprolol released after 3.5h; Y₈ - Percent of metoprolol released after 4.0h; Y₉ - Percent of metoprolol released after 4.5h; Y₁₀ - Percent of metoprolol released after 5.0h; Y₁₁ - Percent of metoprolol released after 5.5h; Y₁₂ - Percent of metoprolol released after 6.0h; Y₁₃ - Percent of metoprolol released after 6.5h; Y₁₄ - Percent of metoprolol released after 7.0h.

Some formulations (E1, E3, E4, E6, E7 – Table IV, Figure 1) released a very low amount of metoprolol within 7 hours. These formulations consisted of a low amount of sodium starch glycolate (5%) with 5% polymer used, in the cases of Eudragit NE (E3) and RS (E6); or they consisted of a higher amount of sodium starch glycolate (20%) with 25% polymer used, in the cases of Eudragit NE (E1) and RS (E4), and with 30% used in the case of Surelease (E6).

The other formulations (E2, E5, E8, E9, E10, E11 – Table IV, Figure 1) released the whole amount of metoprolol quickly, in about one, two or three hours. These formulations consisted of a larger amount of sodium starch glycolate (20%) and low amounts of film - 5% for Eudragit NE (E2) and RS (E5, E10, E11) and 6% for Surelease (E8). The formulation with 5% sodium starch glycolate and 6% Surelease (E9) also developed a rapid release of metoprolol.

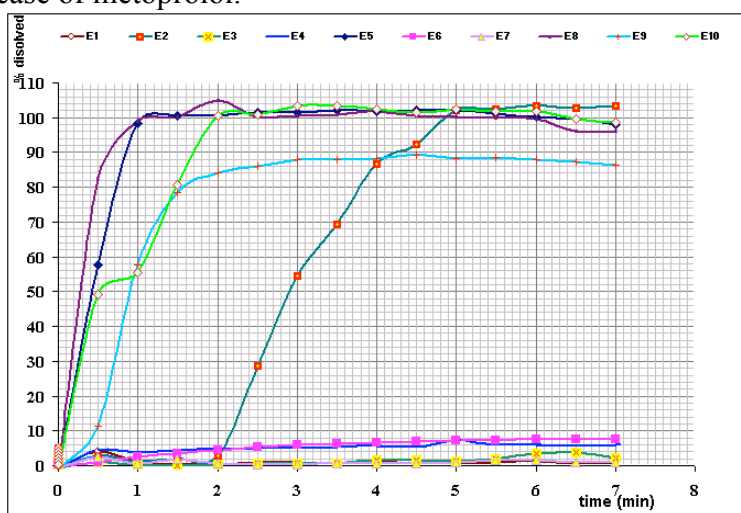


Figure 1
The amount of metoprolol released in time

In the cases where the drug was not released (E1, E3, E4, E6, E7), the amount of sodium starch glycolate was either too low to swell enough in order to break the film, or it was high enough to swell, but the amount of polymer was too large so the film formed was too thick and did not break. In the cases with high amounts of sodium starch glycolate and lower amounts of polymer, the core was able to swell enough to break the thin layer of the film. The exception was E9, which had a small amount of sodium starch glycolate, but was still able to break the thin layer of film, probably because the Surelease film was easier to break than the Eudragit ones.

The influence of the formulation factors on the drug release

Figure 2 shows histograms with the influence of the formulation factors on the $Y_1 - Y_{14}$ responses. The more swelling agent, sodium starch glycolate (X_2), was added, the more active substance was released. In contact with water, sodium starch glycolate swells, causing the nucleus to expand, breaking the polymeric film and releasing the drug.

If higher amounts of sodium starch glycolate was added, the swelling was higher and the film was broken faster.

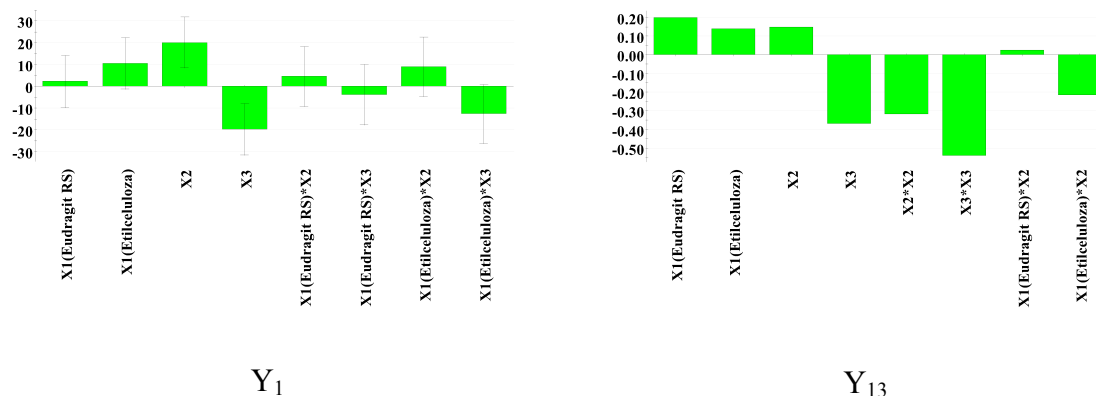


Figure 2

The influence of the formulation factors on the $Y_1 - Y_{14}$ responses
 Y_1 – Percent released after 0.5h; Y_{13} - Percent released after 6.5h. X_1 – Polymer type; X_2 – Sodium starch glycolate amount used; X_3 – Polymer amount used.

Figure 2 also shows that the addition of higher amounts of film forming polymer (X_3) determined less metoprolol released. The amount of polymer determines the thickness of the film, which is water permeable. Water passes through the film, enters the nucleus and causes it to swell and break the film. If higher amounts of polymer are added, the film becomes thicker, so that it is more difficult to break.

The influence of the polymer type (X_1) was not important for the first dissolution times ($Y_1 - Y_3$). After Y_4 , Eudragit RS and ethylcellulose caused a more rapid release than Eudragit NE (in the same amount). This is due to the fact that Eudragit NE is more elastic than Eudragit RS, so that at the same concentration Eudragin RS breaks and releases the drug, while Eudragit NE does not. A method for modifying the elasticity of Eudragit RS is adding a plasticizer (triethylcitrate) [9].

Conclusions

Different types of pulsatile delivery metoprolol minitablets were prepared using three coating polymers. An experimental design plan was employed to study the influence of the polymer type, the polymer concentration and the swelling agent concentration on the drug's *in vitro* release.

Increasing the swelling agent's concentration led to a greater release of metoprolol, due to the expansion of the core which broke the polymeric film. Increasing the polymer concentration decreased the drug release because high amounts of polymer formed thicker films, which could not be broken.

The polymer type did not have a great impact on the release. However, it was found that Eudragit RS is a good candidate for further studies on pulsatile release formulations because it requires the use of a plasticizer. Different amounts of plasticizer can change the film properties, making it more or less elastic, harder or easier to break.

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