DEVELOPMENT OF COMPRESSION COATED TABLETS WITH PULSATILE RELEASE OF METOPROLOL FOR CHRONOTHERAPEUTICAL APPLICATIONS EMPLOYING EXPERIMENTAL DESIGN

ANDREEA LOREDANA VONICA[1], IOAN TOMUŢĂ[2], ADRIANA FECHETE[2], SORIN E. LEUCUŢA[2]

[1]Polipharma Industries S.R.L. Sibiu
[2]Department of Pharmaceutical Technology and Biopharmaceutics, Faculty of Pharmacy, „Iuliu Haţieganu" UMPh Cluj-Napoca

Abstract

Aims. *The aim of this work was to study the reliability of developing metoprolol pulsatile delivery systems for a chronopharmaceutic therapy, by compression coating minitablet cores.*

Materials and methods. *To perform the study an experimental design with three factors and three levels was used. The formulation factors studied were: core type, coating retarding polymer type (hydroxypropyl methylcellulose (HPMC) K15M, HPMC K100M, Carbopol 71G), and filler type (lactose or microcrystalline cellulose). The tablets were studied regarding their in vitro dissolution behavior.*

Results. *According to the obtained results, the lag time period and the release behavior are mainly influenced by the type of the retarding polymer and the type of filler in the coating mixture. In terms of the retarding polymer in the coating mixture, the greatest retarding effect is given by Carbopol 71G NF, followed by HPMC K100M, and HPMC K15M. In terms of the filler, microcrystalline cellulose has a greater retarding effect than lactose, which favors the drug release. Moreover, microcrystalline cellulose leads to obtaining tablets with a lag time of about 2-4 hours, followed by an approximately 0 order kinetics release. Lactose as filler, in combination with Carbopol 71G as retarding polymer, conducts to obtaining tablets with a lag time of 2-4 hours followed by a quick release (approximately 1-1.5 hours).*

Conclusions. *According to the results, a delayed pharmaceutical system with a drug release with a lag time of 2-4 hours can be obtained via compression coating tablets.*

Keywords: compression coated tablets, chronotherapy, experimental design.

DEZVOLTAREA DE SISTEME FARMACEUTICE PULSATILE CU METOPROLOL, PENTRU TERAPIA CRONOFARMACEUTICĂ, CU AJUTORUL MINICOMPRIMATELOR ACOPERITE PRIN COMPRIMARE, UTILIZÂND UN PLAN EXPERIMENTAL

Rezumat

Obiective. *Scopul acestei lucrări a fost studiul viabilităţii dezvoltării unor sisteme farmaceutice pulsatile cu metoprolol, pentru terapia cronofarmaceutică, cu ajutorul minicomprimatelor acoperite prin comprimare.*

Material şi metodă. *S-a utilizat un plan experimental cu trei factori şi trei niveluri pentru a se realiza studiul. Factorii de formulare au fost: tipul nucleului, tipul polimerului de întârziere din stratul extern (hidroxipropil metilceluloza (HPMC) K15M, HPMC K100M, Carbopol 71G) şi tipul diluantului din stratul extern (lactoza sau celuloza microcristalină). A fost studiat comportamentul comprimatelor la dizolvarea in vitro.*

Rezultate. *Din rezultatele obţinute se observă că perioada de latenţă şi tipul eliberării sunt influenţate în special de tipul polimerului de retardare şi de tipul diluantului din învelişul extern. În ceea ce priveşte polimerul de retardare, cel mai mare efect de întârziere este dat de Carbopol 71G NF, urmat de HPMC K100M şi HPMC K15M. În ceea ce priveşte diluantul, celuloza microcristalină are un efect de întârziere mai mare decât lactoza, care favorizează eliberarea medicamentoasă. În plus, celuloza microcristalină conduce la obţinerea de comprimate cu perioadă de latenţă de 2-4 ore, urmate de o eliberare cu o cinetică de aproximativ ordin 0. Utilizarea lactozei ca diluant, în combinaţie cu Carbopol 71G ca polimer de retardare, conduce la obţinerea de comprimate cu perioadă de latenţă de 2-4 ore, urmate de o eliberare rapidă (aproximativ 1-1.5 ore).*

Concluzii. *După rezultatele obţinute, un sistem farmaceutic cu eliberare întârziază cu o perioadă de latenţă de 2-4 ore poate fi obţinut prin utilizarea comprimatelor în comprimat.*

Cuvinte cheie: acoperire prin comprimare, cronoterapie, plan experimental.

1. INTRODUCTION

A pulsatile drug delivery system is characterized by a lag time that is an interval of no drug release followed by rapid drug release. Pulsatile systems are basically time-controlled drug delivery systems in which the system controls the lag time independently of environmental factors like pH, enzymes, gastro-intestinal motility etc. These time-controlled systems can be classified as single unit (e.g. tablet or capsule) or multiple units (e.g. pellets) systems. These systems are designed according to the circadian rhythm of the body. The multiple unit systems like pellets or minitablets are preferred for drug dosage forms because the coating of the medicated units can be formulated to trigger the release in order to comply with the release profile of a pulsatile design [1,2,3,4,5].

It is thought that clinically effective plasma drug concentrations of an antihypertensive medicine, in the early morning, would maximize a drug's effect on blood pressure during that period. Paradoxically, waking to take such a drug in the early morning 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 [6,7,8,9].

A variety of such systems has been proposed over the last two decades and the simplest system is the matrix device where the drug is dispersed within a polymer network. The device may be swellable, hydrophilic, erosion controlled or non-erodible. The latest advances propose the development of more complicated systems in order to improve or adjust the release of the drug in a required time and manner. These can be multilayer systems, core in cup systems and compressed coated systems. Multilayer tablets comprise an active layer containing a matrix core and one or more barriers, applied during tabletting. Core in cup systems usually release drug from a constantly eroding surface as the impermeable cup prevents drug release from the lateral surface. Compressed coated systems completely surround the core with different polymeric barrier-layers. These coatings prevent drug release from the core until the polymeric shell is entirely eroded, dissolved or removed. The delay in drug release depends primarily on covering of the device and secondarily on the core composition. Several systems exhibit a lag time that is dependent on the coating properties. The lag time is frequently followed by a release phase and this characteristic is indicative of pulsatile drug delivery. Combinations of the above devices could be used to further control or modify the release rate of a drug [10,11,12,13,14,15,16,17].

In this paper we have studied the reliability of the development metoprolol pulsatile delivery systems for a chronopharmaceutic therapy, by compression coating of minitablets cores. An experimental design with three factors and three levels was used in order to study the reliability of concept and the influence of the formulation variables on the dissolution release profiles [18,19,20].

2. MATERIALS AND METHODS

2.1. Materials

Metoprolol tartrate (Microsin, Romania); mono-hydrate 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); polyvinylpirrolidone K25 (Merck, Germany); Sodium stearyl fumarate – PRUV (JRS Pharma, Germany), lactose – Tablettose 80M (Meggle, Germany), Isomalt – GalenIQ 721 (Palatinit, Germany), dicalcium phosphate – DiTab (Innophos, USA), hydroxypropyl methylcellulose – HPMC K100M (Colorcon, UK), hydroxypropyl methylcellulose – HPMC K15M (Colorcon, UK), Carbopol 71G NF

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Adress for correspondence: loredana.vonica@umfcluj.ro

(Lubrizol, SUA) , sodium croscarmelose - Ac-Di-Sol (FCM BioPolimers, SUA).

2.2. Experimental Design

A reduced experimental design with three factors and three levels was used to perform the study. 18 experimental determinations were performed according to an experimental plan with three factors and two levels (for one of the factors) and three levels (for the other two factors), in which the formulation variables were qualitative.

The independent variables (formulation factors) and the variation levels are shown in Table I. The dependant variables are shown in Table II.

The experimental design matrix is shown in Table III. The experiments were performed in the order specified in the experimental design matrix.

The experimental design, the coefficient calculation, the statistic parameter calculation and the evaluation of the quality of the fit were performed using the Modde 9.0 software (Umetrics, Sweden).

2.3. Tablet Composition

Three types of tablet cores were prepared, with different diluents excipients: isomalt, microcrystalline cellulose and dicalcium phosphate (C3, C4, and C5). The qualitative and quantitative compositions of the three types

Table I. The Independent Variables and the Formulation Levels.

Formulation Variable	Symbol	Level		
		-1	0	1
Core type	X_1	C3	C4	C5
Retarding polymer in the coating mixture	X_2	HPMC K15M	HPMC K100M	Carbopol 71G NF
Filler in the coating mixture	X_3	Lactose	-	Microcrystalline Cellulose

Table II. Dependent Variables (Answers).

Number	Answer	Symbol
1	The amount of metoprolol released after 0.5h	Y_1
2	The amount of metoprolol released after 1.0h	Y_2
3	The amount of metoprolol released after 1.5h	Y_3
4	The amount of metoprolol released after 2.0h	Y_4
5	The amount of metoprolol released after 2.5h	Y_5
6	The amount of metoprolol released after 3.0h	Y_6
7	The amount of metoprolol released after 3.5h	Y_7
8	The amount of metoprolol released after 4.0h	Y_8
9	The amount of metoprolol released after 4.5h	Y_9
10	The amount of metoprolol released after 5.0h	Y_{10}
11	The amount of metoprolol released after 5.5h	Y_{11}
12	The amount of metoprolol released after 6.0h	Y_{12}
13	The amount of metoprolol released after 6.5h	Y_{13}
14	The amount of metoprolol released after 7.0h	Y_{14}
15	The amount of metoprolol released after 6.5h	Y_{15}
16	The amount of metoprolol released after 8.0h	Y_{16}
17	C_2 - concentration at the first turning point	Y_{17}
18	T_1 – time at the first turning point	Y_{18}
19	C_3 - concentration at the second turning point	Y_{19}
20	T_2 – time at the second turning point	Y_{20}

Table III. Experimental Design Matrix.

Experiment Name	Order of Run	X_1	X_2	X_3
N1	12	C3	HPMC K15M	Lactose
N2	17	C4	HPMC K15M	Lactose
N3	7	C5	HPMC K15M	Lactose
N4	1	C3	HPMC K15M	Microcrystalline Cellulose
N5	14	C4	HPMC K15M	Microcrystalline Cellulose
N6	4	C5	HPMC K15M	Microcrystalline Cellulose
N7	13	C3	HPMC K100M	Lactose
N8	10	C4	HPMC K100M	Lactose
N9	9	C5	HPMC K100M	Lactose
N10	11	C3	HPMC K100M	Microcrystalline Cellulose
N11	15	C4	HPMC K100M	Microcrystalline Cellulose
N12	2	C5	HPMC K100M	Microcrystalline Cellulose
N13	16	C3	Carbopol 71G	Lactose
N14	8	C4	Carbopol 71G	Lactose
N15	5	C5	Carbopol 71G	Lactose
N16	18	C3	Carbopol 71G	Microcrystalline Cellulose
N17	6	C4	Carbopol 71G	Microcrystalline Cellulose
N18	3	C5	Carbopol 71G	Microcrystalline Cellulose

X_1 – core type; X_2 – retarding polymer in the coating mixture; X_2 – filler in the coating mixture.

Table IV. Tablet Core Composition.

	C3		C4		C5	
	mg/cp	**%**	**mg/cp**	**%**	**mg/cp**	**%**
Metoprolol Tartrate	100	41.67	100	41.66	100	41.66
Lactose Monohydrate*	85.02	35.42	85.02	35.42	85.02	35.42
Isomalt	**33.65**	**14.02**	**0**	**0.00**	**0**	**0.00**
Microcrystalline Cellulose	**0**	**0.00**	**33.68**	**14.03**	**0**	**0.00**
Dicalcium Phosphate	**0**	**0.00**	**0**	**0.00**	**33.68**	**14.03**
Sodium Croscarmelose	7.20	3	7.20	3	7.20	3
PVP K30	6.93	2.89	6.93	2.89	6.93	2.89
Fumed Silica	2.40	1	2.40	1	2.40	1
Magnesium Stearate	2.40	1	2.40	1	2.40	1
Sodium Stearyl Fumarate	2.40	1	2.40	1	2.40	1
Total	**240.00**	**100.00**	**240.00**	**100.00**	**240.00**	**100.00**

Table V. Coating Mixture Composition (%).

	Lactose	**Microcrystalline Cellulose**	**HPMC K15M**	**HPMCK100**	**Carbopol 71G NF**	**Magnesium Stearate**	**Total**
1	79		20			1	**100**
2	79			20		1	**100**
3	79				20	1	**100**
4		79	20			1	**100**
5		79		20		1	**100**
6		79			20	1	**100**

of tablet cores are shown in Table IV.

The tablets were obtained by compression using an eccentric press (Korsch EK 0, Germany) equipped with a set of 7 mm biconvex punches. In the first stage metoprolol and lactose were fluid bed granulated using polyvinylpirrolidone K30 [21]. In the second stage, disaggregant (sodium croscarmelose), one of the filler excipients (isomalt/microcrystalline cellulose/dicalcium phosphate) and the lubricant excipients (fumed silica, magnesium stearate, sodium stearyl fumarate) were added to the metoprolol granules and compressed in 240 mg cores, that had a mechanical resistance of 5-11 kg.

2.4. Tablet Coating

The tablets were then coated through compression with a mixture formed of macromolecular polymeric compound and filler excipient. The qualitative and quantitative compositions of the six types of mixtures are shown in Table V.

The tablet coating was obtained by compression using an eccentric press (Korsch EK 0, Germany) equipped with a set of 10 mm biconvex punches. 100 mg of coating mixture were added to the matrix initially, and in the center of the matrix a nucleus minitablet (C3, C4 or C5) was introduced. Next 100 more mg of coating mixture was added and the whole mixture was compressed. The machine was set to obtain 440 mg tablets, with a crushing strength of 5-12 kg.

2.5. *In vitro* dissolution studies

The *in vitro* dissolution tests were done in the PharmaTest PT-DT7 device, which was equipped with the USP no. 2 apparatus (with baskets) employed at 100 rpm rotation speed. The dissolution media used was 500 ml phosphate buffer (pH=6.5) at 37°C. One tablet containing 100 mg metoprolol was 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, 7, 7.5 and 8 hours. Each 5 ml sample was immediately filtered through a 0.45 μm filter and replaced with fresh media to maintain a constant volume across 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.

2.6. Kinetic release evaluation

In order to characterize the dissolution profile regarding lag time release, the empirical equation called Piecewise with three linear segments and two inflexion points was used (Figure 1). The Piecewise equation parameters are: C_1 - minimum concentration, C_2 - concentration at the first inflexion point, C_3 - concentration at the second inflexion point, C_4 - maximum concentration, T_1 - time at the first inflexion point, T_2 - time at the second inflexion point [22]. Using the Piecewise equation, the dissolution profile was divided in three regions (segments): the first segment represents the lag time region, where the percent of drug release was maximum 10%, the second segment represents the region of quick drug release and the third segment represents the region where more than 80% of drug has been released into the dissolution media (Figure 1). So, T_1 (time at the first inflexion point) represents the length of the lag time period and T_2 (time at the second inflexion point) represents the length of the quick drug release period.

The Piecewise equation parameters T_1 (time at the first inflexion point), T_2 (time at the second inflexion point), C_2 (concentration at the first inflexion point), C_3 (concentration at the second inflexion point) can be used as responses of the experimental design for analyzing the

influence of the studied factors on the target dissolution release profile.

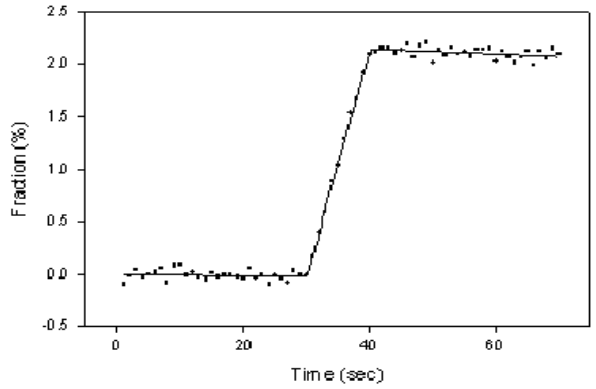


Figure 1. Piecewise function graph.

3. RESULTS AND DISCUSSION

3.1. Results obtained of the tablets cores

Three types of minitablets were manufactured; their composition is presented in Table IV. These minitablets were used as cores that were compression coated. All the three types of minitablets were in accordance with the 7th Ed. European Pharmacopoeia regarding their pharmacotechnical parameters: mass, uniformity of mass, crushing strength, friability, and disaggregation times. The results obtained are shown in Table VI.

The dissolution test was done on the prepared tablets in order to evaluate the *in vitro* release of the drug from the tablets cores. The results obtained are shown in Figure 2.

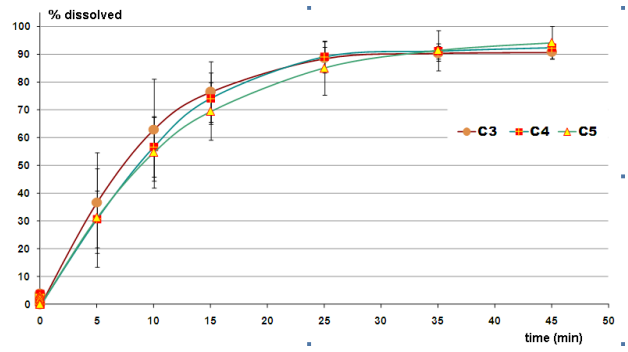


Figure 2. The amount of metoprolol released in time from tablets used as cores.

According to the obtained results, the release from all three types of tablets is quick, the amount of drug released after 30 minutes is over 90% in all cases.

According to the obtained results all the three types of minitablets used as cores have good pharmacotechnical properties. The results obtained for the pharmacotechnical parameters were much under the limits specified by the 7th Ed. European Pharmacopoeia regarding friability and disaggregation time, while the crushing strength was within the imposed limits. Regarding the *in vitro* release, the amount dissolved after 30 minutes is more than 90% of the drug contained in the tablets. Moreover, there are no significant differences between the three types of tablets regarding the pharmacotechnical results and the *in vitro* release.

3.2. Metoprolol release from coated tablets

The matrix of results is shown in Table VII. The results indicate that the amount of metoprolol released differs from formulation to formulation and it depends on the formulation factors studied in the experimental design. The metoprolol release profiles from compression coated tablets are shown in Figure 3.

Some formulations only released a very small amount of metoprolol in the 8 hours; these were the formulations where the coating was done with Carbopol 71G as a retarding polymer in the coating mixture and microcrystalline cellulose as filler in the coating mixture. Other formulations released the whole amount of drug in approximately 2 hours without a lag time; these were the formulations in which the coating was done with HPMC K15M as a retarding polymer in the coating mixture and lactose as filler in the coating mixture. A part of the formulations released the drug more or less rapidly after a lag time; these were usually the formulations in which the coating was done with HPMC K100M as a retarding polymer in the coating mixture and microcrystalline cellulose as filler in the coating mixture.

Table VI. Results obtained when determining the pharmaco-technical parameters of the minitablet cores.

Series	Average Mass (mg)	Friability (%)	Mechanical Resistance (kg)		Disintegration Time (minutes)
	mg ±5%	Maximum 1.0%	Minimum 5kg		Maximum 15 min
C3		0.123%	Average	7.44	5.25 min
	241		Minimum	6.20	
	(216-264)		Maximum	11.20	
C4		0.343%	Average	8.25	6.04 min
	250		Minimum	5.90	
	(216-264)		Maximum	10.40	
C5		0.239%	Average	8.66	4.76 min
	243		Minimum	6.40	
			Maximum	12.10	

Table VII. Matrix of results.

Time	Y1	Y2	Y3	Y4	Y5	Y6	Y7	Y8	Y9	Y10	Y11	Y12	Y13	Y14	Y15	Y16	Y17	Y18	Y19	Y20
(min)	0.5	1	1.5	2	2.5	3	3.5	4	4.5	5	5.5	6	6.5	7	7.5	8				
N1	57.27	86.10	94.57	99.64	99.33	98.53	97.64	98.57	99.50	99.85	99.92	99.91	99.86	99.83	99.81	99.81	10.24	0.11	89.82	1.06
N2	87.53	99.03	101.15	101.96	97.82	98.76	99.70	100.64	101.58	101.65	101.61	101.55	101.50	101.50	101.50	101.50	12.28	0.07	99.53	0.60
N3	54.92	73.14	93.16	96.65	96.70	97.63	98.57	99.50	100.45	100.83	101.04	101.06	101.05	101.05	101.05	101.05	13.33	0.12	93.73	1.20
N4	0.10	0.40	1.96	2.18	8.17	11.16	15.46	20.50	24.58	30.67	34.25	39.63	43.06	46.70	50.96	54.33	8.50	4.62	39.70	6.06
N5	0.18	1.99	1.97	7.02	10.50	12.14	15.82	20.38	25.48	30.11	35.50	40.50	43.93	47.74	53.46	55.61	9.58	2.62	88.06	11.53
N6	0.02	0.20	0.20	0.70	0.99	1.21	1.58	2.04	2.55	3.01	3.55	4.05	4.39	4.77	5.35	5.56	9.12	10.85	30.00	32.00
N7	6.09	29.67	62.45	91.69	98.39	100.29	101.32	102.61	101.84	103.40	104.05	103.68	102.72	101.65	102.91	100.84	9.68	0.53	93.68	2.03
N8	47.35	76.45	89.53	96.53	100.12	101.89	101.94	102.32	102.57	103.04	105.05	103.03	103.05	101.49	100.69	99.71	12.40	0.17	100.10	2.55
N9	8.23	22.22	41.47	57.04	63.49	67.86	76.49	89.47	89.67	96.39	101.74	104.92	104.03	103.71	103.25	102.07	11.18	0.65	103.57	5.41
N10	2.73	2.77	3.89	5.87	9.17	11.73	15.40	20.64	25.62	30.11	34.83	38.84	43.73	48.25	53.41	57.30	8.88	2.74	88.00	11.23
N11	1.14	1.53	2.79	4.40	10.91	11.64	14.90	19.97	24.29	28.06	34.81	37.95	42.16	46.82	51.00	54.57	9.42	2.84	78.00	10.41
N12	2.99	3.86	3.61	5.11	8.62	10.98	15.16	21.60	25.11	28.73	33.75	36.68	40.87	45.78	50.73	54.01	8.29	2.77	75.00	10.39
N13	0.10	1.17	1.07	1.58	28.27	42.03	48.06	52.05	55.68	57.39	59.47	62.27	64.73	66.39	67.76	69.11	1.61	2.01	44.92	2.81
N14	0.54	1.38	1.55	3.33	5.10	5.62	10.17	14.33	26.39	48.44	56.04	62.16	67.59	71.62	73.86	75.68	8.85	3.82	91.73	6.68
N15	0.36	0.36	1.27	2.34	4.53	7.42	12.23	16.25	22.69	26.99	38.55	48.89	57.34	61.31	66.92	0.36	7.43	3.57	89.00	9.38
N16	0.06	0.84	1.30	3.26	2.16	3.22	6.18	9.80	13.34	16.80	21.13	25.08	30.03	35.69	43.80	0.06	9.80	4.50	88.00	12.83
N17	0.11	0.12	0.25	1.15	1.76	3.25	4.60	6.09	8.19	12.63	15.56	18.54	22.18	27.32	30.91	0.11	9.20	5.04	90.00	16.00
N18	0.65	0.66	0.19	0.86	1.10	2.39	3.56	5.09	8.40	10.19	13.05	20.86	34.42	47.24	58.25	0.65	13.52	6.06	93.35	9.76
N19	0.68	0.17	0.28	1.84	1.96	3.21	4.69	6.41	8.52	11.26	14.65	18.10	29.81	37.22	40.77	0.68	10.24	0.11	89.82	1.06
N20	0.70	0.78	0.41	0.89	1.97	2.34	3.10	5.75	8.95	11.91	14.09	20.08	35.22	49.86	61.90	0.70	12.28	0.07	99.53	0.60

Y_1 - Percent of metoprolol released after 0.5h; Y_2 - Percent of metoprolol released after 1.0h; Y_3 - Percent of metoprolol released after 1.5h; Y_4 - Percent of metoprolol released after 2.0h; Y_5 - Percent of metoprolol released after 2.5h; Y_6 - Percent of metoprolol released after 3.0h; Y_7 - Percent of metoprolol released after 3.5h; Y_8 - Percent of metoprolol released after 4.0h; Y_9 - Percent of metoprolol released after 4.5h; Y_{10} - Percent of metoprolol released after 5.0h; Y_{11} - Percent of metoprolol released after 5.5h; Y_{12} - Percent of metoprolol released after 6.0h; Y_{13} - Percent of metoprolol released after 6.5h; Y_{14} - Percent of metoprolol released after 7.0h; Y_{15} - Percent of metoprolol released after 7.5h; Y_{16} - Percent of metoprolol released after 8.0h;Y_{17} - C_2 concentration at the first turning point; Y_{18} - T_1 time at the first turning point; Y_{19} – C_3 - concentration at the second turning point; Y_{20} – T_2 – time at the second turning point.

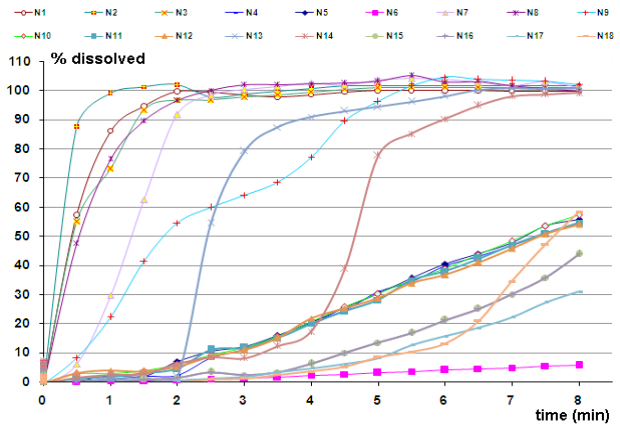


Figure 3. The amount of metoprolol released in time from delayed release delivery system.

3.3. Experimental design analysis. Quality of fit

The statistical module from the Modde 9 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. Both R^2 and Q^2 values are numbers, ranging from 0 to 1. Values close to 1 for both R^2 and Q^2 indicate a very good model with an excellent predictive power R^2 and Q^2 give the best summary of the fit of the model. R^2 represents the overestimated measures and Q^2 represents the underestimated values of the quality of fit of the model [1,10].

The results obtained after the fit and after the statistical parameters calculation using the data obtained in the experimental plan are shown in Figure 4. R^2 was over 0.85 for all the results. Q^2 was over 0.7 for all results. With one exception (Y_7), the validity of the model was over 0.75. The reproducibility was over 0.8 for the majority of the results (with the exceptions of Y_2 and Y_{16}). The results of the ANOVA test showed that p for the model was less than 0.05 for all the experiments, and p for the error was over 0.05 for all the experiments.

3.4. Experimental design analysis. Influence of formulation factors on dissolution profile (responses Y_1 – Y_{16})

Figure 5 shows the influence of the formulation factors on the Y_1 – Y_{16} answers. According to the obtained results, at the first times of release (Y_1 – Y_4), the nucleus type does not influence the amount of drug released. This means that the type of filler excipient used to prepare the cores does not influence the drug release from coated tablets in the first 2 hours. Between 2.5 and 4.5 hours (Y_5 – Y_9), using isomalt as a filler excipient leads to the increase of the amount of drug released, and using dicalcium phosphate leads to the decrease of the amount of drug released (Y_5 – Y_6).

In terms of the retarding polymer in the coating mixture (X_2), the greatest retarding effect is given by Carbopol 71G NF, followed by HPMC K100M and HPMC K15M. In terms of the intensity of the effects, it was found that the difference between the two cellulose based polymers is much smaller than the difference between the cellulose based polymers and Carbopol, the latter having a much stronger retarding effect. Moreover, the tablets prepared with Carbopol as a retarding excipient had a certain tendency of sticking to the matrix and punches.

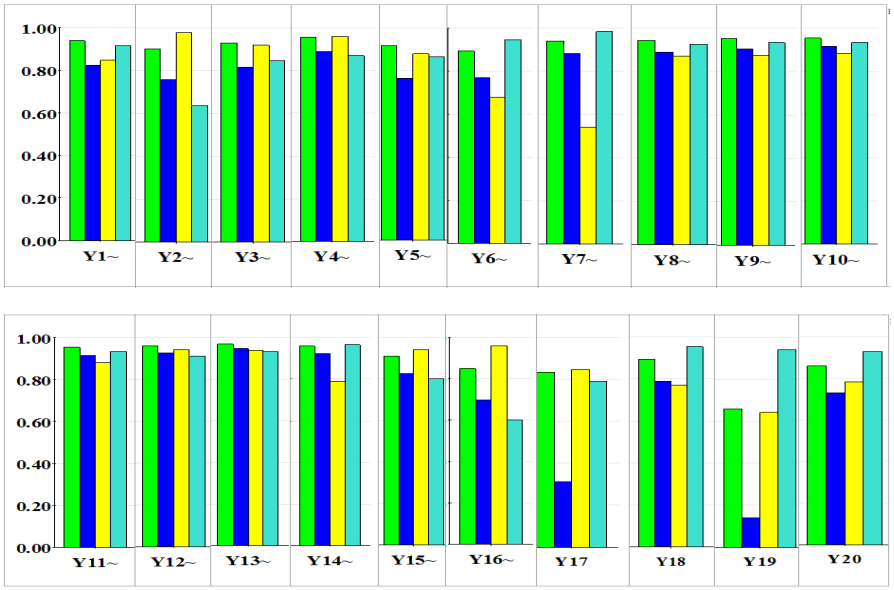
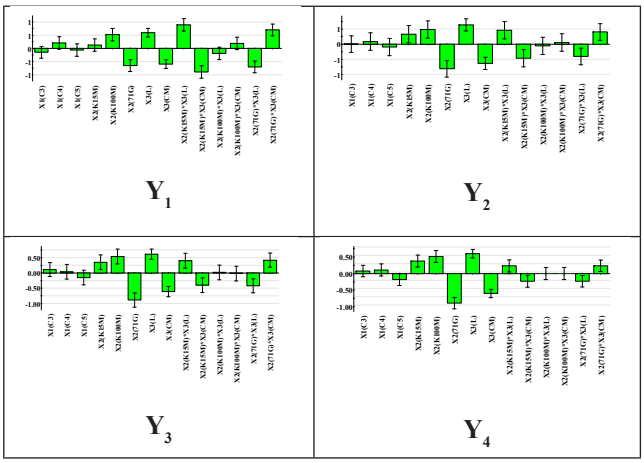


Figure 4. The results obtained at the data fit.
Y_1 - Percent of metoprolol released after 0.5h; Y_2 - Percent of metoprolol released after 1.0h; Y_3 - Percent of metoprolol released after 1.5h; Y_4 - Percent of metoprolol released after 2.0h; Y_5 - Percent of metoprolol released after 2.5h; Y_6 - Percent of metoprolol released after 3.0h; Y_7 - Percent of metoprolol released after 3.5h; Y_8 - Percent of metoprolol released after 4.0h; Y_9 - Percent of metoprolol released after 4.5h; Y_{10} - Percent of metoprolol released after 5.0h; Y_{11} - Percent of metoprolol released after 5.5h; Y_{12} - Percent of metoprolol released after 6.0h; Y_{13} - Percent of metoprolol released after 6.5h; Y_{14} - Percent of metoprolol released after 7.0h; Y_{15} - Percent of metoprolol released after 7.5h; Y_{16} - Percent of metoprolol released after 8.0h;Y_{17} - C_2 concentration at the first turning point; Y_{18} - T_1 time at the first turning point; $Y_{19} – C_3$ - concentration at the second turning point; $Y_{20} – T_2$ – time at the second turning point.

Bearing in mind the stronger retarding effect of HPMC K100M, it is recommended for use as a retarding agent in the coating mixture.

Lactose monohydrate and microcrystalline cellulose were used as filler excipients in the coating mixture. The influence of the filler in the coating mixture on the drug release is shown in Figure 5. According to the obtained results, microcrystalline cellulose has a greater retarding effect compared to lactose, which favored the drug release. In all the formulations, the percent of drug released in the first hours was greater in the cases where lactose was used as a filler excipient. The percent was greatest in the cases when the other excipient in the retarding mixture was HPMC K15M (formulations N1, N2 and N3). This can be explained by the fact that lactose, a water soluble excipient, combined with HPMC K15M, which has a low viscosity, does not form a retarding layer that is able to stop the drug release from the nucleus. Instead, the association of microcrystalline cellulose, a water insoluble excipient, with HPMC in the coating layer, leads to obtaining a coating layer that stops the drug release from the nucleus. The effect is that much stronger with higher viscosity HPMC (using HPMC K100M). Moreover, using microcrystalline cellulose lead to obtaining tablets with a lag time of about 2 hours, after which the release was controlled with an approximately 0 order kinetics (formulations N5, N10, N11 and N12). Instead, using lactose as a filler excipient in the coating mixture, together with a strong retarding polymer (Carbopol 71G), leads to obtaining tablets which have a relatively quick release (approximately 1-1.5 hours) after a lag time of about 2 hours (formulation N13) and about 4 hours (formulation N14). Using microcrystalline cellulose as a filler excipient in the coating mixture with a strong retarding polymer (Carbopol 71G) leads to obtaining tablets with a lag time of about 4 hours, after which the release is controlled with an approximately 0 order kinetics (formulations N16 and N17).



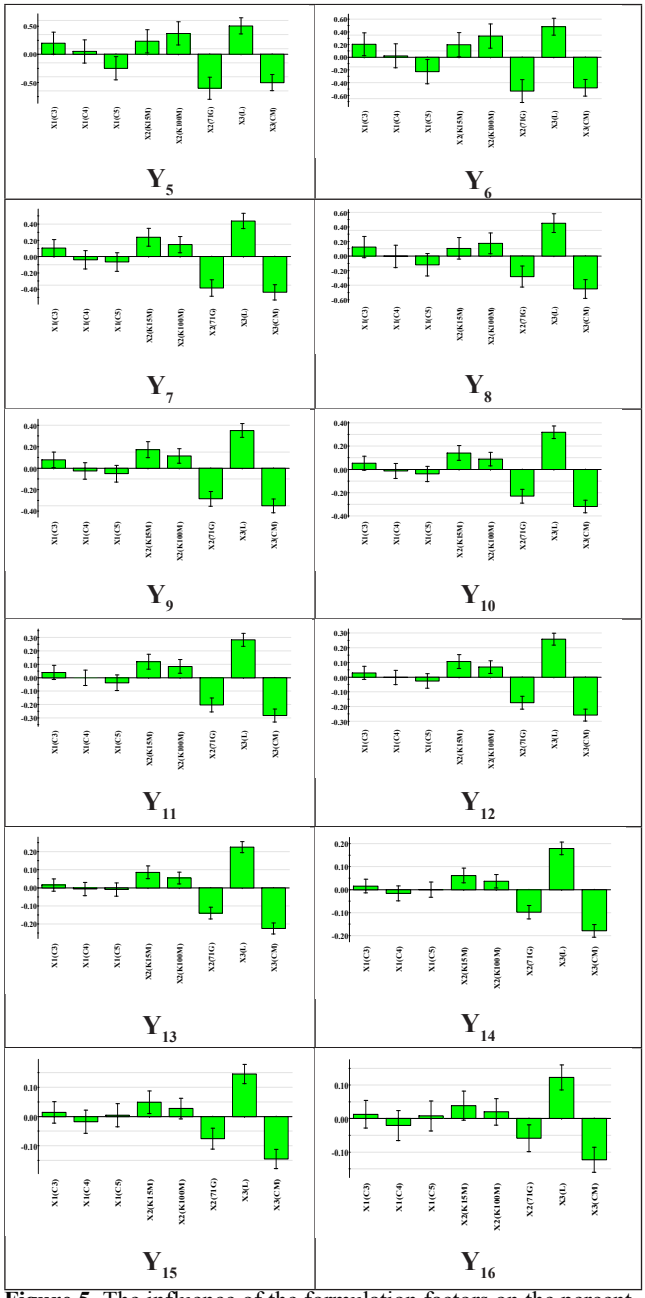


Figure 5. The influence of the formulation factors on the percent of metorolol release at different time intervals (Y_1 – Y_{16} answers)
Y_1 - Percent of metoprolol released after 0.5h; Y_2 - Percent of metoprolol released after 1.0h; Y_3 - Percent of metoprolol released after 1.5h; Y_4 - Percent of metoprolol released after 2.0h; Y_5 - Percent of metoprolol released after 2.5h; Y_6 - Percent of metoprolol released after 3.0h; Y_7 - Percent of metoprolol released after 3.5h; Y_8 - Percent of metoprolol released after 4.0h; Y_9 - Percent of metoprolol released after 4.5h; Y_{10} - Percent of metoprolol released after 5.0h; Y_{11} - Percent of metoprolol released after 5.5h; Y_{12} - Percent of metoprolol released after 6.0h; Y_{13} - Percent of metoprolol released after 6.5h; Y_{14} - Percent of metoprolol released after 7.0h; Y_{15} - Percent of metoprolol released after 7.5h; Y_{16} - Percent of metoprolol released after 8.0h.
X_1 – core type; X_2 – retarding polymer in the coating mixture; X_3 – filler excipient in the coating mixture.

3.5. Experimental design analysis. Influence of formulation factors on Piecewise equation parameters

Figure 6 shows the influence of the formulation factors on the Piecewise equation parameters (Y_{17} - C_2 - concentration at the first inflexion point; Y_{18} - T_1 - time at the first inflexion point; Y_{19} – C_3 - concentration at the second inflexion point; Y_{20} – T_2 - time at the second inflexion point).

Figure 6 shows that Y_{17} (C_2 - concentration at the first inflexion point) is influenced only by the interactions between the studied factors. Y_{17} decreases when using a combination of HPMC K15M with lactose, or a combination of Carbopol 71G with microcrystalline cellulose. Y_{17} increases when using a combination HPMC K15M with microcrystalline cellulose, or a combination of Carbopol 71G with lactose.

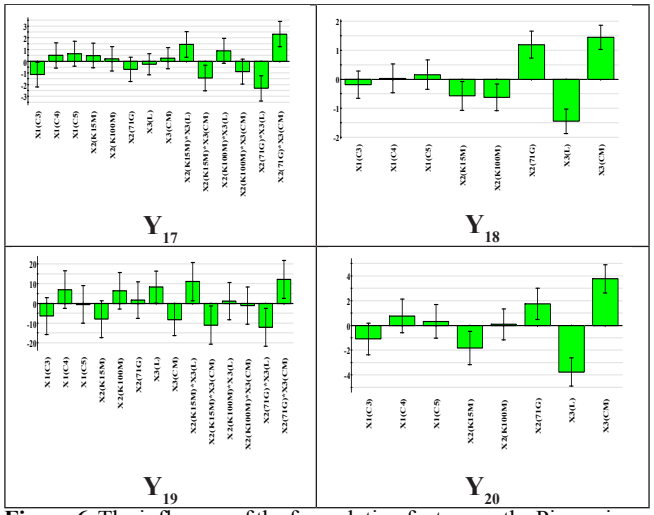


Figure 6. The influence of the formulation factors on the Piecewise equation parameters (Y_{17} – Y_{20} answers)
Y_{17} - C_2 concentration at the first turning point; Y_{18} - T_1 time at the first turning point; Y_{19} – C_3 - concentration at the second turning point; Y_{20} – T_2 – time at the second turning point
X_1 – core type; X_2 – retarding polymer in the coating mixture; X_3 – filler excipient in the coating mixture.

According with the obtained results, Y_{18} (T1 - the time at the first inflexion point) is influenced by X_2 (retarding polymer in the coating mixture) and X_3 (filler excipient in the coating mixture). X_1 (nucleus type) has no influence on Y_{18}. Figure 6 shows that Y_{18} increases when using microcrystalline cellulose as filler and also when using Carbopol 71G as retarding polymer. Y_{18} decreases when using lactose as filler and also when using HPMC K15M or K100M as retarding polymers.

In the same way as response Y_{17} (C_2 - concentration at the first inflexion point), Y_{19} (C_3 - concentration at the second inflexion point) is influenced only by the interactions between the studied factors. Figure 6 shows that Y_{19} decreases when using a combination of HPMC K15M with lactose, or a combination of Carbopol 71G

with microcrystalline cellulose. Y_{19} increases when using a combination of HPMC K15M with microcrystalline cellulose, or a combination of Carbopol 71G with lactose.

In the same way as response Y_{18} (T_1 - the time at the first inflexion point), Y_{20} (T_2 - time at the second inflexion point) is influenced only by X_2 (retarding polymer in the coating mixture) and X_3 (filler excipient in the coating mixture). Figure 6 shows that Y_{20} increases when using microcrystalline cellulose as filler and also when using Carbopol 71G as retarding polymer. Y_{20} decreases when using lactose as filler and also when using HPMC K15M or K100M as retarding polymers.

4. CONCLUSIONS

A study was completed in order to evaluate the possibility of obtaining delayed release systems of a compression coated tablet type. In order to do this, an experimental plan with three factors and three levels was used to study the way that the release of metoprolol from compression coated tablets is influenced by:

1. the nucleus (core) type (the excipient used to prepare the nucleus);
2. the retarding polymer in the coating mixture;
3. the type of filler in the coating mixture.

According to the obtained results, a delayed pharmaceutical system which has a drug release with a lag time of 2-4 hours (and probably even more) can be obtained via compression coating tablets.

The lag time period and release behavior are influenced especially by the retarding polymer and the type of filler in the coating mixture. Using Carbopol 71G as retarding polymer, in combination with lactose as filler, conducts to obtaining a delayed pharmaceutical system with a lag time of 2-4 hours and a quick release (approximately 1-1.5 hours). Using Carbopol 71G or K100M as retarding polymer, in combination with microcrystalline cellulose as filler, conducts to obtaining a delayed pharmaceutical system with a lag time of 2-4 hours and with an approximately 0 order release kinetics.

Based on the observations noted, it is possible to prolong the lag time in order to obtain a certain desired formulation. In order to obtain a longer lag time period (5-6 hours) and a quick release after the lag time, more investigations are needed using Carbopol 71G as retarding polymer and lactose as filler and a thicker coating layer.

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