OPTIMIZATION OF METOPROLOL TARTRATE MODIFIED RELEASE MATRIX TABLETS FORMULATION USING SURELEASE AS BINDER FOR GRANULATION

CRISTIAN ALECU[1], IOAN TOMUȚĂ[2*], DANA DUDAS[2], SORIN LEUCUȚA[2], CONSTANTIN MIRCIOU[3]

[1] SC Laropharm SRL, Bucuresti, Romania
[2]University of Medicine & Pharmacy „Iuliu Haţieganu", Cluj-Napoca, Romania
[3] University of Medicine & Pharmacy„Carol Davila", Bucharest, Romania
** corresponding author: tomutaioan@umfcluj.ro*

Abstract

The aim of this experimental work was to evaluate the influence of formulation variables on drug (metoprolol tartrate) release during a period of 12 hours, using a statistical method, in order to prepare sustained release matrix type tablets. A full factorial experimental design with two factors and three levels was used. The formulation factors were the matrix-forming polymer concentration (hydroxypropylmethylcellulose) and the granulation polymer concentration (ethylcellulose). The dependent variables were the percent of metoprolol released at different periods of time and *k* release constant and *n* exponent of the Peppas equation.

The obtained results have shown that the percentage of the drug released during the study period was influenced by both polymers used, increasing their percentages leading to a prolonged time of the released drug. However there are differences in the period of their influence, the management of this behavior being of practical interest in the optimization of the release rate.

Rezumat

Obiectivul acestei lucrări experimentale a fost evaluarea influenţei variabilelor de formulare (procentul de HPMC (hidroxipropilmetilceluloza) – Methocel K100 M şi de Surelease E7 19010) asupra procentului de metoprolol tartrat cedat la diferite intervale de timp, precum şi asupra cineticii de cedare, utilizând o metodă statistică. Pentru a realiza acest lucru s-a folosit un plan experimental factorial complet, cu 2 factori şi 3 nivele. Factorii de formulare studiaţi au fost concentraţia polimerului formator de matriţă (hidroxipropilmetilceluloza) şi concentraţia polimerului de granulare (etilceluloza). Variabilele dependente au fost procentul de metoprolol cedat la diferite intervale de timp şi constanta de cedare k şi exponentul n din ecuaţia lui Peppas.

Rezultatele obţinute au arătat că procentul de substanţă medicamentoasă cedată pe parcursul studiului a fost influenţat de ambii polimeri utilizaţi, creșterea procentului de Surelease crește procentul de metoprolol cedat, în timp ce creșterea procentului de Methocel scade procentul de metoprolol cedat. Preocuparea pentru acest comportament al amestecurilor de polimeri este în continuare de mare interes pentru optimizarea cedării substanțelor medicamentoase de tipul metoprololului.

Keywords: metoprolol, Surelease, extended release matrix, experimental design

Introduction

Metoprolol is used in the treatment of several diseases of the cardiovascular system due to its selectivity in blocking the β1 receptors. Its high solubility determines a short half-life (3-5 hours) and a rapid drug release. Therefore, metoprolol is often used as extended-release dosage forms which are designed to release the drug gradually, allowing a reduction in the frequency of administration.

Coated beads, osmotic pumps and matrix tablets are some of the important classes of oral extended-release dosage forms currently in use, the matrix tablets being the easiest approach among these classes. The retarding materials that are commonly used include: hydrophobic 'plastic' materials, e.g. ethyl cellulose, methacrylic acid copolymers; insoluble, erodible materials, e.g. waxes, hydrogenated vegetable oils; hydrophilic polymers, e.g. sodium alginate, cellulosic polymers [1-5].

Hydroxypropyl cellulose (HPC) and hydroxypropyl methylcellulose (HPMC) are hydrophilic cellulose ethers polymers frequently used for oral controlled delivery. HPMC is available in several grades that vary in extent of substitution of hydroxypropoxy and methoxy groups and in viscosity, the hydration rate (i.e. gel formation rate) increasing with increasing hydroxypropoxy group substitutions [6,7]. In oral products, it is primarily used as a matrix in extended-release tablet formulations [8,9]. Surelease is an extended release, aqueous coating system utilizing ethylcellulose as the rate controlling polymer for drug release. The primary means of drug release is by diffusion through the Surelease membrane and is directly controlled by film thickness. By simply increasing or decreasing the amount of Surelease applied, the rate of drug release is modified. It can be used as binder, together with the hydrophilic polymer used for matrix formation [10].

In this study we intended to assess the influence of formulation variables (HPMC – Methocel K100 M and Surelease E7 19010 amount) on drug release from tablets over a 12-hour period, as well as their influence on the kinetic release. The analysis of the experimental design was realised using optimization module from Modde 9.0 software, Umetrics, Sweden.

Materials and Methods

Apparatus. Fluid bed granulator (Aeromatic A.G., Switzerland); tablet press (Korsch EK-0 Germania), mass volumetric test apparatus SVM (Erweka, Germany); DIN sieve set (VEB MLW, Germany); analytical balance (Sartorius, Switzerland); tablet hardness test apparatus Monsanto (Monsanto, Italy); tablet disintegration test apparatus ZT 2 (Erweka, Germany); tablet friability test apparatus TA (Erweka, Germany).

Materials. Metoprolol tartrate (Microsin, Romania); Lactose monohydrate 200 mesh - (Meggle, Germany); Microcrystallin cellulose PH102 – (JRS, Germany); Polyvinyl pyrolidone – PVP K30 (BASF Germany); Hydroxypropylmethylcellulose - Methocel K100 M (Colorcon, UK); Lactose DC – Tabletoza 80M (Meggle,Germany); Silicon dioxide – Aerosil 200 (Degussa, Germany); Magnesium stearate (Merck, Germany); Surelease E7 19010 (Colorcon, UK).

Methods. *Granules preparation.* Granules were manufactured by a fluid bed granulator (Aeromatic A.G., Switzerland) according to the granulation formula listed in Table I. The binder solution, Surelease E7 19010 used in aqueous dispersions of different concentrations (4%, 8% and 12%), was sprayed by atomization under the working conditions listed in Table II. The granules obtained after ending the atomization of the binder solution were dried for 30 minutes, at 60^{o}C in the same apparatus.

Table I
Granulation formula

Compound	**%(m/m)**
Metoprolol tartrate	27.78
Lactose monohydrate	30
Surelease E7 19010*	4-8-12
Distilled water	q.s.

*according with experimental design matrix (Table V)

Table II
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 (^{0}C)	70
Outlet Air Temperature (^{0}C)	27-33
Spraying duration (min)	25

Tablets preparation. The granules were mixed with compression excipients, the compression formula being presented in Table III. Tablets were manufactured by an eccentric tablet press Korsch EK0 equipped with a 10 mm diameter lenticular set punch. The tablet press was adjusted so that the compressed tablets had an average mass of 450 mg corresponding to a concentration of 100 mg metoprolol tartrate/tablet.

Table III
Compression formula

Compound	%(m/m)
Metoprolol granules*	53
Methocel K100 M**	20-30-40
Lactose DC	25-15-5
Silicon Dioxide	1
Magnesium Stearate	1

*according with the composition shown in Table I
** according with the experimental design matrix (Table V)

Experimental Design. The study was conducted according to a full factorial experimental design with two factors and three levels. Modde 9.0 optimization program, Umetrics, Sweden was used for the experimental design construction, coefficients and statistical parameters computation and fitting of the experimental data in order to evaluate the results. Table IV presents the independent variables (formulation and process variables) and their level of variation, the experimental design matrix is shown in Table V and Table VI illustrates the dependent variables.

Table IV
Independent Variables (Formulation and Process Variables)

Variables		Levels		
	Symbol	-1	0	+1
SURELEASE concentration (%)	X_1	4	8	12
METHOCEL concentration (%)	X_2	20	30	40

Table V
The Experimental Design Matrix

Exp Name	X_1	X_2
N1	4	20
N2	4	30
N3	4	40
N4	8	20
N5	8	30
N6	8	40
N7	12	20
N8	12	30
N9	12	40
N10	8	30

X_1 – % SURELEASE, X_2 – %METHOCEL

Table VI
Dependent variables

No.	Results	Symbol
1	% released at 1 hour	Y_1
2	% released at 2 hours	Y_2
3	% released at 3 hours	Y_3
4	% released at 4 hours	Y_4
5	% released at 6 hours	Y_5
6	% released at 8 hours	Y_6
7	% released at 12 hours	Y_7
8	k Peppas	Y_8
9	n Peppas	Y_9

Determination of the dependent variables. The percentage of metoprolol tartrate released at different times (1, 2, 3, 4, 6, 8, 12 hours) and the coefficients of Peppas kinetic equation (k and n) represented the dependent variables in this research study.

Metoprolol release from the prepared matrix tablets was assessed by dissolution testing in accordance with Eur.Ph.: apparatus no. 2 (blades) was used at a rotation speed of 50 rpm; the release study was performed in 900 mL phosphate buffer pH 6.8; the concentrations of dissolved drug were spectrophotometrically determined at 275nm. Sampling times were: 1, 2, 3, 4, 6, 8 and 12 hours.

Kinetic release evaluation. To determine the release kinetics, fitting the experimental data with different mathematical equations: first order, zero order [11], Korsmeyer-Peppas [12,13], Hixson-Crowell [14] and Baker-Lonsdale were performed. Kinetic equations used for fitting the experimental data are shown in Table VII.

For the computation of release kinetics, only a value greater than 80% was considered. If the correlation coefficient is close to 1 [15,16] and Akaike index value is smaller [12,17], release kinetics is considered adequate.

Table VII
Release models tested

Baker-Lonsdale	$(3/2)[1-(1-(Q_t/Q_\infty)^{2/3}]-(Q_t/Q_\infty)=Kt$
Korsmeyer – Peppas	$Q_t/Q_\infty=K_k t^n$
Hixson-Crowell	$Q_0^{1/3}-Q_t^{1/3}=K_s t$
Higuchi	$Q_t/Q_\infty=K_k t^{0.5}$
First Order	$Q_t/Q_\infty=K_k t$
Zero Order	$Q_t=Q_0+K_0$t

Results and Discussion

Table VIII and Figure 1 illustrate the results obtained after *in vitro* dissolution of the matrix tablets prepared according to the experimental design. The influence of the formulation factors, namely the percentage of Methocel and the type of polymer coating, on the properties of the resulted granules and tables are specified in the matrix of the results (Table VIII).

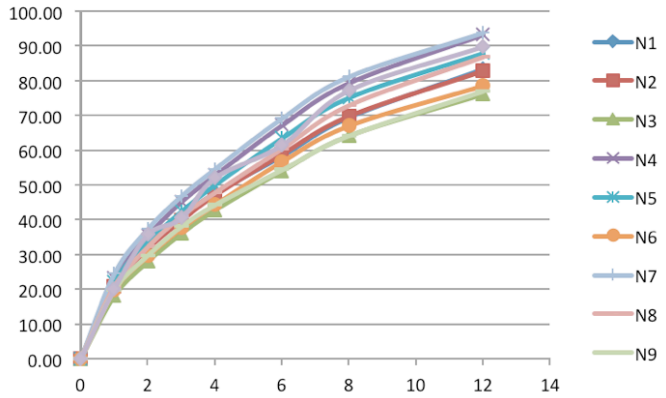

Figure 1
Drug dissolution profiles of formulations made according to the experimental design

Experimental Design Analysis. Goodness of Fit. In making and analyzing the experimental design the optimization program Modde 9.0 (Umetrics, Suedia) was used [18]. Fitting the experimental data and calculating the statistical parameters for the validation of the experimental design was performed with the same program, using the **Partial Least Squares (PLS)** method. The reliability of the experimental design was verified by calculating the following statistical parameters: R^2, Q^2, ANOVA test and dependence curves [18,19]. 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 excellent predictive power. A value of R^2 validity under 0.25 represents a proper fitting. A value of Q^2 reproducibility under 0.5 represents a weak process control [18,19].

Table VIII
Matrix of the results

Exp name	Y_1	Y_2	Y_3	Y_4	Y_5	Y_6	Y_7	Y_8	Y_9
N1	21.85	32.81	41.01	47.69	58.32	69.47	83.40	22.848	0.5255
N2	20.87	31.61	39.74	47.01	58.82	69.80	82.83	22.043	0.5408
N3	18.11	28.06	36.08	42.81	54.10	64.23	76.22	19.568	0.5569
N4	23.16	35.48	45.20	52.86	67.27	79.41	93.38	24.878	0.5425
N5	22.17	33.76	42.53	50.11	63.57	75.28	88.09	23.656	0.5397
N6	19.78	29.66	37.62	44.43	56.81	67.16	78.69	20.864	0.5450
N7	24.52	37.41	46.84	54.64	69.20	81.23	93.89	26.502	0.5210
N8	20.86	32.23	40.99	47.81	60.44	72.94	86.88	22.082	0.5590
N9	19.84	29.82	38.14	44.34	54.44	64.24	77.07	21.054	0.5279
N10	20.17	35.76	40.53	52.11	61.57	77.28	89.91	23.076	0.5576

Y_1 – released at 1 hour, Y_2 – released at 2 hours, Y_3 – released at 3 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

Figure 2 shows the results obtained after fitting and calculating the statistical parameters R^2 and Q^2 by using data acquired through the experimental design.

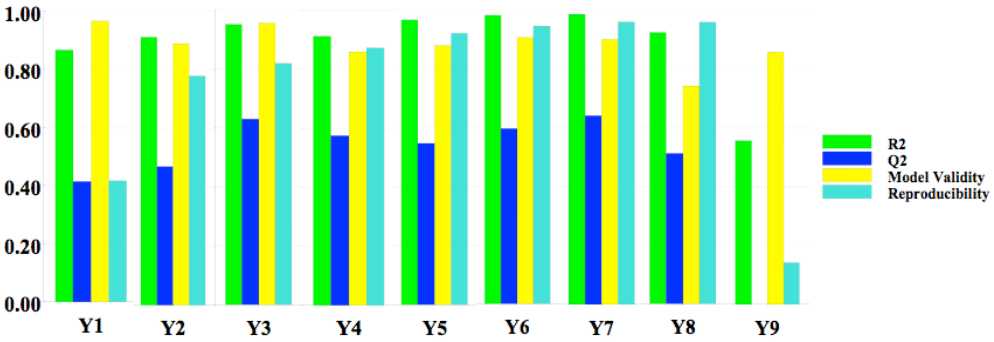

Figure 2

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_{12} – n Peppas

According to available data, the results fit well for Y_1-Y_8 responses. It was not obtained a satisfactory fitting for Y_9 response. The results of ANOVA test show that the experimental data obtained are due to changing the formulation factors: „p" for model is lower than 0.05 and „p" for residual is greater than 0.05, for all responses [18,19]. The results of ANOVA test showed that the experimental data obtained 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).

Analysis of the influence of formulation factors on the active substance release from tablets for a period of 12 hours. Table VIII illustrates the results obtained after *in vitro* dissolution of the matrix tablets prepared according to the experimental design.

The effect of factors and the effect of interactions between factors on responses are reflected by equation coefficients used for fitting the experimental data [18,19]. They are represented graphically as histograms and isoresponse curves. The histograms from Figure 3 and isoresponse curves from Figure 4 show the differences between the active substance release from tablets for a period of 12 hours due to formulation factors. The purpose of Surelease in the formulation was to cover metoprolol particles during the granulation process in order to reduce the release rate of metoprolol. Surelease's amount increase thickens the coating on metoprolol particles and thus the polymer film becomes stronger and less permeable.

The necessary time for water penetration will be longer and the dissolution of metoprolol, will be retarded, leading to the decrease of the drug release.

Methocel (the second formulation factor) acts as matrix forming polymer, allowing drug release as the matrix erodes. An increase in the amount of Methocel reduces the percentage of metoprolol dissolved for all times of determination and thus, the drug release.

The increase of Methocel K100 M amount reduced the rate of the drug released after 1, 2 and 4 hours. The analysis of coefficients shows that only the percentage of Methocel (X_2) influences the percentage of the drug released after 1, 2 and 4 hours. The percentage of the polymer used for granulation (Surelease) is not significant.

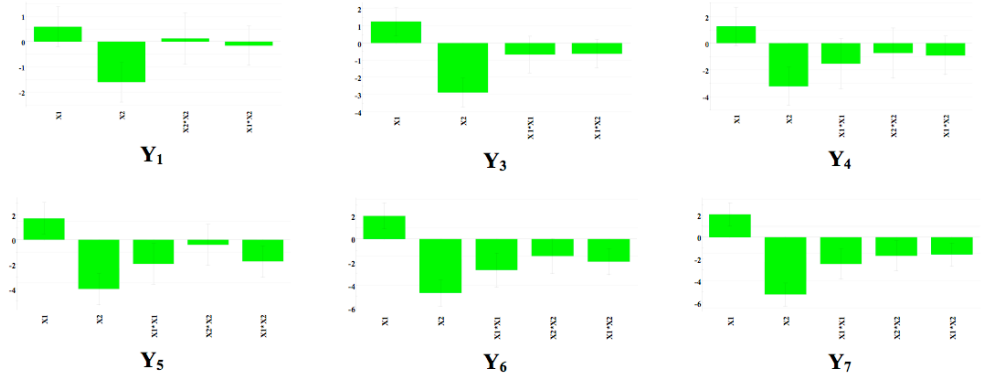

Figure 3

The influence of the formulation factors on the active substance release from tablets. X_1 – % Surelease, X_2 – % METHOCEL, Y_1 – released at 1 hour, Y_3 – released at 3 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

But for all the rest of investigated times (3, 6, 8, 12 hours), the percentage of the drug released is influenced by the percentage of Surelease (X_1), as well as the percentage of Methocel K100 M (X_2); increasing the amount of Surelease (used as a binder) increases the percentage of the drug released, while increasing the amount of Methocel K100 M (matrix forming polymer) reduces the percentage of the drug released. The intensity of the influence of the first formulation factor X_1 (the amount of Surelease used as a binder) is lower than that of X_2 factor (the amount of Methocel K100 M) at all determination times.

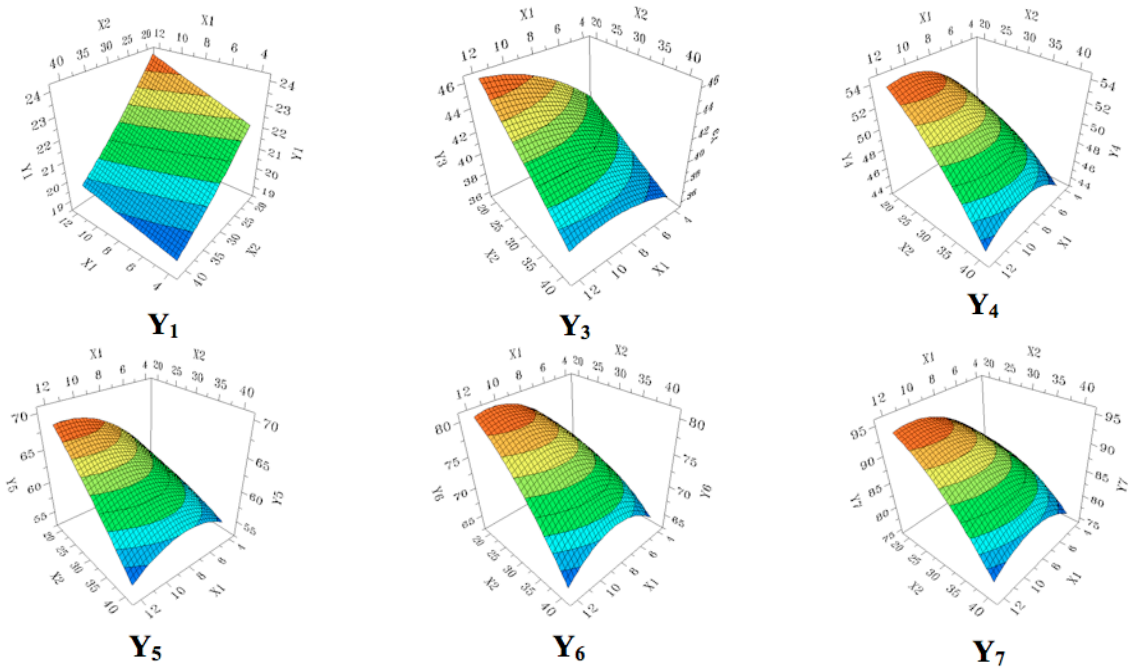

Figure 4

The influence of the formulation factors on the active substance release from tablets. Y_1 – released at 1 hour, Y_2 – released at 2 hours, Y_3 – released at 3 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

The increase of the percentage of the drug released when increasing the amount of Surelease occurs when using a small percentage of Methocel (20%). The explanation could be the following: when increasing Surelease amount, the polymer thickness increases and film plasticity decreases. Decreased plasticity makes the polymer to become brittle and break in the moment of compression, if the percentage of Methocel is low. So, at *in vitro* release evaluation, increasing the percentage of Surelease at low Methocel concentrations (20%) has the effect of increased metoprolol release at 3, 6, 8, 12 hours. On the other hand, for increased Methocel percentages (40%), the percentage of the released drug is not significantly affected by the amount of Surelease (Figure 3).

The influence of X_1 formulation factor on the release does not have the same intensity at all times studied (it has a significant influence only at 3, 6, 8, 12 hours) and the influence is linear in the experimental field. In contrast with X_1, X_2 formulation factor (the amount of Methocel K100 M) effect on release has nearly 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 6, 8 and 12 hours. There is a strong interaction between X_1*X_1 and X_1*X_2 at 6 hours, and at 8 and 12 hours appears also the X_2*X_2 interaction, which increases in intensity between these last two times. Concurrent increase of Surelease amount (X_1) and Methocel K100 M amount (X_2) decrease the percentage of the drug released at 6, 8 and 12 hours. There are no interactions between the formulation factors studied at 1-4 hours.

Therefore, the percentage of the drug released during the 12 hours is influenced both by Methocel amount (X_2) and Surelease amount (X_1): increasing the percentage of Surelease leads to the increase of the percentage of the released drug and increasing the percentage of Methocel leads to the decrease of the percentage of the released drug. Also, the percentage of Surelease (X_1) has no influence on drug release at 1, 2, 4 hours, it appears only at 3, 6, 8 and 12 hours; in contrast with Surelease, the influence of Methocel K100 M concentration is almost the same at all sampling times.

Other researchers achieved similar results regarding release extension of drugs by polymers. Nellore et al. prepared tablets containing different amounts of HPMC (10-40%) and studied the effect of HPMC amount on release rate of metoprolol from tablets prepared by direct compression. The increase of HPMC percentage from 10% to 40% significantly delayed the release of metoprolol tartrate from tablets [2].

Sakellariou et al. showed that HPMC is incompatible with ethylcellulose, leading to inhomogeneous films [1,20], which may explain the different influence of Surelease amount on release depending on HPMC concentration. Muschert et al. achieved a decrease of diltiazem HCl release from pellets coated with thin ethylcellulose film, unlike the results obtained in this study [21].

The results show that the increase of HPMC amount can lead to formulations with a satisfactory drug release rate.

Kinetic release analysis. Table IX illustrates the results obtained after fitting the data with different kinetic equations. For all formulations, the best fit of the *in vitro* release data was obtained for Peppas model. For this reason, the responses introduced in the experimental design were the two parameters of Peppas equation (k and n).

Equation coefficients used for fitting the experimental data obtained at kinetic release evaluation are represented graphically as histograms and isoresponse curves in Figure 5.

Table IX

The results obtained from fitting the data with different kinetic equations

		N1	N2	N3	N4	N5	N6	N7	N8	N9	N10
Baker and Lonsdale	k	0.0138	0.0135	0.0108	0.0184	0.0160	0.0120	0.0196	0.0147	0.0114	0.0163
	r2	0.9790	0.9747	0.9740	0.9653	0.9703	0.9751	0.9699	0.9668	0.9820	0.9609
	AIC	30.402	31.740	31.160	35.178	33.529	31.190	34.228	34.093	28.645	35.637
Peppas	k	22.848	22.043	19.568	24.878	23.656	20.864	26.502	22.082	21.054	23.076
	n	0.5255	0.5408	0.5569	0.5425	0.5397	0.5450	0.5210	0.5590	0.5279	0.5576
	r2	0.9993	0.9984	0.9978	0.9976	0.9974	0.9973	0.9967	0.9984	0.9990	0.9942
	AIC	12.179	17.087	18.443	21.360	20.967	19.836	23.109	17.824	13.590	26.253
Hixon and Crowell	k	0.0451	0.0446	0.0385	0.0557	0.0504	0.0412	0.0586	0.0473	0.0397	0.0510
	r2	0.9511	0.9620	0.9579	0.9827	0.9740	0.9574	0.9793	0.9754	0.9391	0.9781
	AIC	35.387	34.152	34.010	31.053	32.749	34.365	32.021	32.325	35.817	32.209
Higuchi	K	23.970	23.802	21.781	26.950	25.489	22.707	27.565	24.677	22.188	25.723
	r2	0.9983	0.9961	0.9936	0.9951	0.9952	0.9946	0.9960	0.9939	0.9978	0.9899
	AIC	15.245	20.525	22.848	23.555	22.634	22.097	22.179	23.973	15.989	27.588
First order	K	0.1613	0.1589	0.1354	0.2006	0.1806	0.1460	0.2118	0.1688	0.1403	0.1826
	r2	0.9797	0.9863	0.9841	0.9933	0.9917	0.9842	0.9924	0.9912	0.9731	0.9904
	AIC	30.212	28.114	28.250	25.403	25.953	28.512	26.026	26.187	31.013	27.313
Zero order	k	8.4223	8.3818	7.6889	9.4912	8.9726	8.0006	9.6720	8.7163	7.7980	9.0815
	r2	0.7354	0.7683	0.7985	0.7708	0.7647	0.7754	0.7201	0.8032	0.7406	0.7974
	AIC	44.815	44.372	42.897	45.879	45.293	43.754	46.804	44.257	43.865	44.989

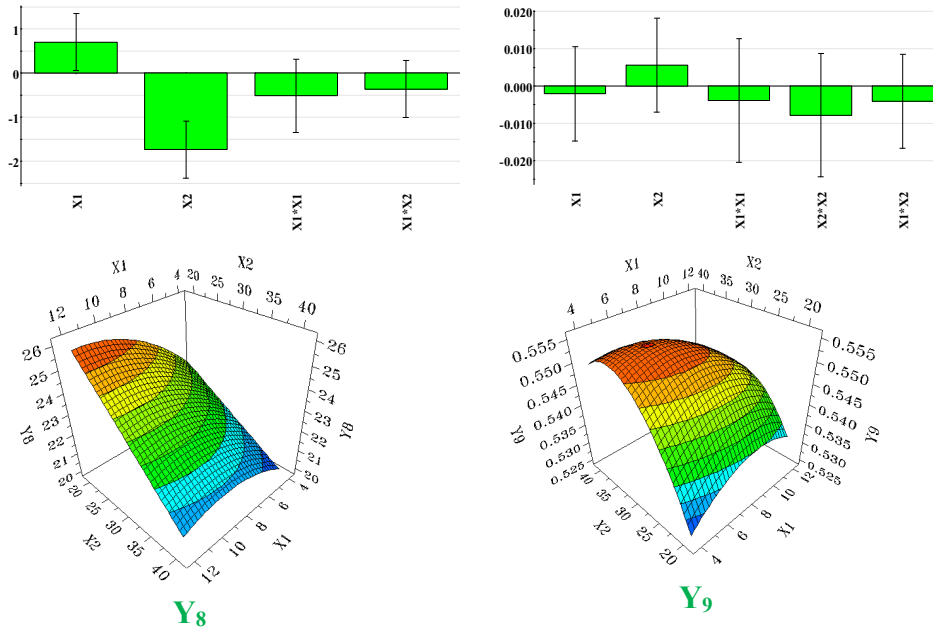

Figure 5

The influence of the formulation factors on kinetic release, Y_8-Y_9

Y_8 – k Peppas, Y_9 – n Peppas

X_1 and X_2 formulation factors affect the k Peppas parameter, as shown by the analysis of the coefficients. The influence of the formulation factors on the parameter k Peppas is similar to their influence on the *in vitro* release of metoprolol.

Surelease concentration (X_1) has a directly proportional effect on k Peppas parameter: increasing the amount of the granulation polymer increases the release percentage of metoprolol and also k Peppas value. The results achieved by other researchers are similar, showing that k Peppas release constant decreases with increased polymer concentration (Kollidon SR) [22].

Methocel concentration (X_2) has an inversely proportional effect on k Peppas parameter and on metoprolol release, respectively: increasing HPMC K100 M concentration, decreases the k Peppas value and also the metoprolol release. The effect of X_2 factor is stronger in intensity compared to the X_1 factor and the intensity of X_2 factor influence is linear in the experimental field. Unlike X_2, the intensity of X_1 factor influence is not linear in the experimental field. For low Methocel percentages, the intensity increases with the increase of the granulation polymer concentration, whereas at high Methocel percentages, the intensity is maximum around 8%, after which the intensity of the influence decreases. There are no interactions between the formulation factors studied. No correlation was found between the formulation factors studied and n Peppas parameter, meaning that n Peppas parameter does not depend on the formulation factors studied.

Based on information from the literature, drug kinetic release from HPMC matrix tablets is complex. It is based on swelling, diffusion and erosion processes and on Korsmeyer-Peppas mathematical model [23,24]. The release from HPMC matrix tablets occurs in three stages: the entering of the dissolution medium inside the matrix (hydration) represents the first stage; the second stage is the swelling and concurrent or subsequent matrix erosion; the transport of the dissolved drug through the hydrated polymer or the matrix fragments transport to the dissolution medium represents the third stage [1-4,6]. The drug release from the tablets prepared with the two polymers (HPMC K 100M and Surelease) occurs after a Higuchi model. The best linearity was obtained for the Higuchi model, indicating that the drug release from the matrix occurs as a process dependent on the square root of time, based on Fick diffusion. Similar results were achieved by other researchers. Harris et al. found that the release kinetics of ibuprofen from HPMC matrix corresponds to the Higuchi model [17], but regarding the *n*

Peppas value, the release mechanism cannot be estimated with certainty, due to a complex mechanism of swelling, diffusion and erosion [16].

Conclusions

Methocel amount (X_2) and Surelease amount (X_1) influence the percentage of the drug released during the 12 hours: increasing the percentage of Surelease leads to the increase of the percentage of the released drug and increasing the percentage of Methocel leads to the decrease of the percentage of the released drug.

The percentage of Surelease (X_1) has no influence on drug release at 1, 2, 4 hours, it appears only at 3, 6, 8 and 12 hours; in contrast with Surelease, the influence of Methocel K100 M concentration is almost the same at all sampling times.

The release is influenced by metoprolol diffusion and the erosion of the matrix, this being proven by the fact that the kinetic release of all studied formulations fitted best with Peppas model.

No correlation was found between the studied formulation factors (Methocel amount and Surelease amount) and the n Peppas parameter, suggesting that this parameter is not influenced by the studied formulation factors.

References

1. Thakkar VT, Shah PA, Soni TG, Parmar MY, Gohel MC, Gandhi TR. Goodness-of-Fit Model-Dependent Approach for Release Kinetics of Levofloxacin Hemihydrates Floating Tablet. *Dissolution Technologies* 2009, 16(1), 35-39.
2. Grassi M, Grassi G. Mathematical Modelling and Controlled Drug Delivery: Matrix Systems. *Current Drug Delivery* 2005, 2, 97-116.
3. Gohel MC, Panchal MK, Jogani VV. Novel Mathematical Method for Quantitative Expression of Deviation from Higuchi Model. *AAPS PharmSciTech* 2000, 1(4), article 31.
4. Frenning G. Theoretical analysis of the release of slowly dissolving drugs from spherical matrix systems. *Journal of Controlled Release* 2004, 95, 109-117.
5. Tomuta I, Leucuta SE. The influence of formulation factors on the kinetic release of metoprolol tartrate from prolong release coated minitablets. *Drug Development and Industrial Pharmacy,* 2007, 33(10), 1071-1077.
6. Siepmann F, Siepmann J, Walther M, MacRae RJ,Bodmeier R. Polymer blends for controlled release coatings. *Journal of Controlled release* 2008,125, 1-15.
7. Mircia E, Sipos E, Imre S, Avrigeanu V, Hancu G, Iantovics B, Balaci T, New modified release tablets with pentoxifylline based on lipophilic matrix. Note 1. Formulation, physical study and determination of dissolution profiles of the active substance from the proposed formulations, *Farmacia*, 2012, 60(2), 218-226
8. Mehta RY, Tiwari SB, Cabelka T, Bernthal H, Farrel TP, Rajabi-Siahboomi A. The Utility of Ultra-High Viscosity Hypromellose in Extended Release Matrix Formulations. *Technical NotesColorcon*,2010.
9. Rahman M, Ahsan Q, Kumar Jha M, Rahman Moghal M, Rahman H. Development and in-vitro evaluation of sustained release matrix tablets of Salbutamol sulphate using Methocel

K100M CR polymer. *International Journal of Pharma. Research & Development*, 2011, 2(3), 567-576.
10. Rege PR, Fegely KA, Scattergood LK, Rajabi-Siahboomi AR. Predictability of Drug Release from Multiparticulate Systems Coated with an Aqueous Ethylcellulose Dispersion. Modified Release Technologies, Technical NotesColorcon, 2005.
11. Wagner JG. Interpretation of percent dissolved-time plots derived from in vitro testing of conventional tablets and capsules.*J. Pharm. Sci*. 1969, 58, 253–1257.
12. Korsmeyer RW, Gurny R, Doelker EM, Buri P, Peppas NA.Mechanism of solute release from porous hydrophilic polymers. *Int. J. Pharm*. 1983,15, 25–35.
13. Peppas NA.Analysis of Fickian and non-Fickian drug release from polymers.*Pharm. ActaHelv.*1985,60, 110–111.
14. Hixson AW, Crowell JH. Dependence of reaction velocity upon surface and agitation. *Ind. Eng. Chem*.1931,23, 923–931.
15. Dressman J. Kramer J. Pharmaceutical Dissolution Testing, Taylor & Francis, London, 2005
16. Sood A, Panchagnula R.Role of dissolution studies in controlled release drug deliverysystems, S.T.P. *Pharm Sci*., 1999, 9(2), 175-168.
17. Prasacu I, Mircioiu C, Sandulovici R, Enache F.Release of metoprolol from solid dosage forms. Choice and validation of theoretical model. *Farmacia*, 2009, LVII(1), 89-98.
18. Eriksson L, Johansson E, Kettaneh-Wold N, Wikstrom C, Wold S.*Design of Experiments: Principles and Applications*. Umetrics Academy, Umea, 2000.
19. *** MODDE 9Software for Design of Experiments and Optimization: User's Guide and Tutorial. Umetrics Academy Inc, Umea, 2010.
20. Siepmann F, Hoffman A, Leclercq B, Carlin B, Siepmann J. How to adjust desired drugs release patterns from ethylcellulose-coated dosage forms. *Journal of Controlled release* 2007,119, 182-189.
21. Muschert S, Siepmann F, Leclercq B, Carlin B, Siepmann J. Prediction of drug release from ethylcellulose coated pellets. *Journal of Controlled release* 2009,135, 71-79.
22. Strübing S, Metz H,Mäder K. Characterization of poly(vinyl acetate) based floating matrix tablets. *Journal of Controlled release*,2008,126, 149-155.
23. Shoaib MH, Tazeen J, Merchant HA and Yousuf RI. Evaluation of drug release kinetics from ibuprofen matrix tablets using HPMC. *Pak. J. Pharm. Sci*. 2006, 19(2), 119-124.
24. Siepmann J,Siepmann F. Mathematical modeling of drug delivery. *International Journal of Pharmaceutics* 2008,364, 328-343.

Manuscript received: December 12th 2012