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PHARMACEUTICAL TECHNOLOGY

DEVELOPMENT AND *IN VITRO* EVALUATION OF MULTIPARTICULATE SUSTAINED RELEASE CARBAMAZEPINE FORMULATION

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Abstract: The objective of the present study was the development and the *in vitro* evaluation of extended release multiparticulate dosage forms with carbamazepine, starting from drug crystals of established granulometry as cores and using Eudragit NE aqueous dispersions as coating film polymer in a bottom spray fluid bed coating system. The chosen independent variables, i.e., the quantity of film coating (Eudragit NE) and the % of hydrophilic polymer in film coating that act as pores generating (hydroxypropyl methylcellulose ratio) were optimized with a two-factor, three-level central composite experimental design. The chosen dependent variables were cumulative percentage values of carbamazepine released after 1, 2, 4, 6, 8 and 12 h and Peppas kinetic release equation parameters (k and n). Based on the experimental design, different carbamazepine formulations were proposed and their release profiles were determined. The second-order polynomial model coefficients and response surface plots were used to analyze the relation between the dependent and the independent variables. The optimized formulation prepared according to computer-determined levels provided a release profile which was close to the predicted values. The dissolution profile of carbamazepine from the coated crystals and tablets prepared with them were similar, and were unchanged after storage for 3 months under controlled conditions.

Keywords: carbamazepine, sustained release, multiparticulate system, experimental design, optimization, Eudragit NE

Carbamazepine is an antiseizure agent and has also proved effective in the treatment of trigeminal neuralgia (1). Although the half-life of carbamazepine is relatively long, ranging between 25 and 85 h after a single dose, its effect is substantially reduced after repeated dosing due to autoinduction. The cytochrome P450-mediated formation of carbamazepine-10,11-epoxide is prominent pathway of carbamazepine metabolism (2). Due to its increased metabolism, pronounced daily fluctuations in the serum concentration of carbamazepine are observed and are a cause for concern. The therapeutic blood serum concentration range of carbamazepine is about 4–12 μg/mL. Blood levels of carbamazepine below 4 μg/mL have been found to be ineffective in treating clinical disorders and conversely blood levels greater than 12 μg/mL have been found to increase the chances of side-effects, such as neuromuscular disorders, cardiovascular and gastrointestinal effects. Currently, the dosage regimes for conventional carbamazepine formulations typically require 3–4 doses per day in order to maintain effective blood concentration. This is very bothersome for ambulatory patients, and often leads to poor patient compliance (3, 4).

Sustained release dosage forms have been the focus of research for improved therapy, both through improved patient compliance and decreased incidences of adverse drug reactions (4, 5).

For sustained-release dosage forms containing very high quantities of the active pharmaceutical ingredient, like carbamazepine, it is particularly critical to avoid an excessively rapid release (dose dumping) as that can lead to undesirable toxic effects. Moreover, such systems are dependent upon gastric emptying rates and transit times, and can be associated with significant intra-and inter-individual variations. These disadvantages have led to a shift in modified release technology from the use of monolithic systems to multiple unit systems in which each individual unit is formulated with modified release characteristics (6).

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Multiple unit dosage forms have a more constant gastric empting rate, possess a large surface area, which advantageously promotes complete and uniform absorption, minimizes peak plasma fluctuations and thus reduces the potential for systemic side effects. A further advantage of these dosage forms is that high local concentrations of the active substance in the system are avoided as a consequence of the units being distributed freely throughout the tract. The multiple unit dosage form ensures incorporation of higher dose resulting in a decreased dosing frequency and consequently better patient compliance (7).

Our previous studies have shown the possibility to prepare sustained release preparations by film coating of pellets or minitablets with polymethacrylates polymers, the formulation of them being facilitated by the use of design of experiments and optimization procedures (8). 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, Eudragit NE 40D is a high flexibility polymer that requires no plasticizer. It is insoluble but swellable in water and has low permeability (9). Drug release from extended release dosage forms coated, reservoir type, coated with insoluble polymers may be modified by additives that dissolve on exposure to biological fluids and thus make coating porous (10). To increase the permeability characteristics of that coating, suitable hydrophilic polymers such as hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC) or polyethylene glycol as pores generating may be used (10–13). In our study, to increase permeability characteristics of the coating film, hydroxypropyl methylcellulose (HPMC) Methocel E 5 LV was used. To study the influence of the amount of hydroxypropyl methylcellulose in coating film on carbamazepine release from coated crystals, the HPMC ratio in coating film was introduced in experimental design as formulation factor.

The aim of the study was to develop a pharmaceutical technological process in order to obtain extended release multiparticulate dosage forms with carbamazepine starting from carbamazepine crystals as cores and using Eudragit NE as coating film polymer in a bottom spray fluid bed coating system.

Table 1. Independent variables (formulation factors).

Variables	Symbol	Levels		
		–1	0	1
Eudragit NE ratio	X_1	7	14	21
HPMC* ratio	X_2	0	12.5	25

*Methocel E 5 LV

Table 2. The matrix of the experimental design.

Exp. No.	Run order	X_1	X_2
N1	1	7	0
N2	6	21	0
N3	5	7	25
N4	4	21	25
N5	11	7	12.5
N6	3	21	12.5
N7	9	14	0
N8	7	14	25
N9	10	14	12.5
N10	2	14	12.5
N11	8	14	12.5

X_1 – Eudragit ratio; X_2 – HPMC ratio

Table 3. Dependent variables (results).

Reponses	Symbol
Cumulative % carbamazepine released in 1 h	Y_1
Cumulative % carbamazepine released in 2 h	Y_2
Cumulative % carbamazepine released in 4 h	Y_3
Cumulative % carbamazepine released in 6 h	Y_4
Cumulative % carbamazepine released in 8 h	Y_5
Cumulative % carbamazepine released in 10 h	Y_6
Cumulative % carbamazepine released in 12 h	Y_7
k – Peppas	Y_8
n – Peppas	Y_9

Table 4. Coating formula.

Excipients	Amount (g) / %
Carbamazepine crystals, fraction 250–600 μm	180 g
Eudragit NE 40D*	7–21%*
HPMC***	0–25%**
Talcum	30%**
Water	50%****

* percent of carbamazepine crystals loading . ** percent of excipients in dry film. *** Methocel E 5LV. **** percent of water reported to the amount of Eudragit NE 40D.

Table 5. Working conditions

Parameters	Value
Method (type)	bottom spray
Charge load (g)	180
Time of pre-heating, (min)	1
Nozzle diameter (mm)	0,8
Spaying rate (g/min)	5
Atomizing pressure (bar)	2.8–3.0
Spraying time (min)	20–50
Inlet air temperature (^oC)	36–42
Outlet air temperature (^oC)	30–33
Fan air (m^3/min)	4–5
Drying temperature (^oC)	40
Time of final drying (min)	30

EXPERIMENTAL

Materials

Carbamazepine (Fabrica Italiana Sintetici, Italy), Eudragit NE 40D (Rohm Pharma Polymers, Germany), hydroxylpropyl methylcellulose (HPMC) – Methocel E 5LV and Methocel E 15LV (Dow Chemical, UK), talcum (S&D Chemicals, UK), silicon dioxide – Aerosil (RohmPharma Polymers, Germany), simeticone (Colorcon, UK), magnesium stearate (Merck, Germany).

Apparatus

Fluid bed coater Strea 1 in Wurster configuration (Aeromatic A.G., Switzerland), Ultra Turrax (Janke and Kunkel, Germany), dissolution apparatus PT-DT7 (PharmaTest, Germany), HPLC with UV detection (Agilent 1100Series, SUA), DIN sieve set (VEB MLW, Germany), tablet press EK-0 (Korsch, Germany), tablet hardness test apparatus Monsanto (Italy), tablet disintegration test apparatus ZT 2 (Erweka, Germany), stability testing cabinet (Binder, Germany).

Experimental design

In order to perform the study a central composite experimental design with two factors and three levels was used (14, 15). The independent variables (Table 1) were the ratio of polymeric film used for coating (Eudragit NE 40D) and the ratio of pore generating excipient in polymeric insoluble films (low viscosity hydroxypropyl methylcellulose

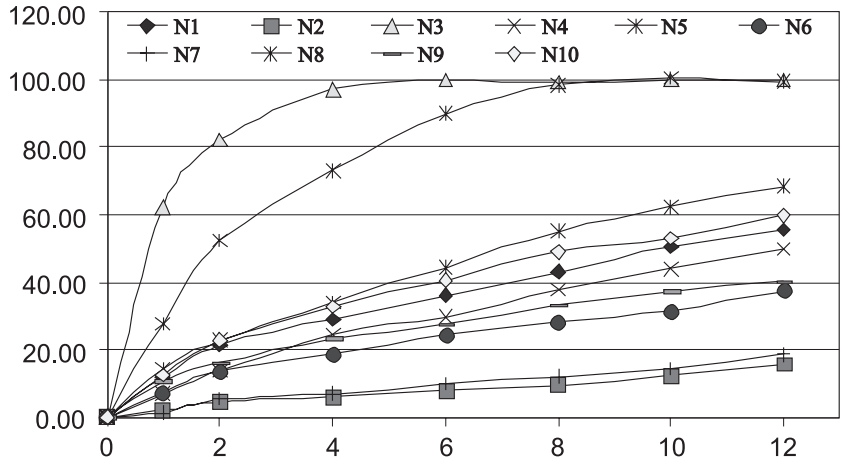

Figure 1. The results obtained at *in vitro* release of the carbamazepine from experimental formulations $N_1 – N_{10}$. $N_1 – N_{10}$ formulations perfomed according to the experimental design matrix (Table 2)

Table 6. Tablets preparation formula (qualitative and quantitative).

	N8		N5	
	mg / tablet	%	mg/tablet	%
Coated crystals*	244	69.71	253	72.29
Microcrystalline cellulose	67.5	19.29	58.5	16.71
HPMC (Methocel E 15LV)	35	10.00	35	10.00
Magnesium stearate	3.5	1.00	3.5	1.00

* equivalent to 200 mg carbamazepine

– Methocel E 5 LV). The matrix of the experimental design is presented in Table 2. The dependent variables (Table 3) were the percent of drug release at different time intervals and the Peppas equation parameters: k – kinetic release constant and n – exponent.

Construction of the experimental design, computation of the coefficients, statistical parameters and fitting of the experimental data have been performed using Modde 6.0 optimization program (Umetrics, Sweeden) (15).

Coating of the carbamazepine crystals

The carbamazepine crystals (sieved fraction of 250–600 μm) were coated with Eudragit NE 40D (an insoluble but permeable polymeric film) in a fluidized bed coating device (Strea 1, Aeromatic Filder). The ratio of film formatting polymer (Eudragit NE 40D) and the ratio of the excipient for pores generating in insoluble film (HPMC) were different from one experiment to another according to the experimental design matrix. The composition of coating formula is shown in Table 4. To prepare the coating suspension, first HPMC was dissolved in water and then talc was suspended in water and homogenized (Ultra Turrax); this suspension was poured into Eudragit NE 40 D shortly before use. After passage through a 0.25 mm sieve, the mixture was processed with continuous gentle stirring during spray coating. The technological parameters during the coating process are shown in Table 5. The curing treatment was performed at the end of coating process, directly in fluid bed apparatus at 40°C for a 30 min time period.

Tablets preparation

Control release tablets with carbamazepine, were achieved by compression of the selected coated carbamazepine crystals (formulation N8 and N optim) by using an eccentric tablet press. The com-

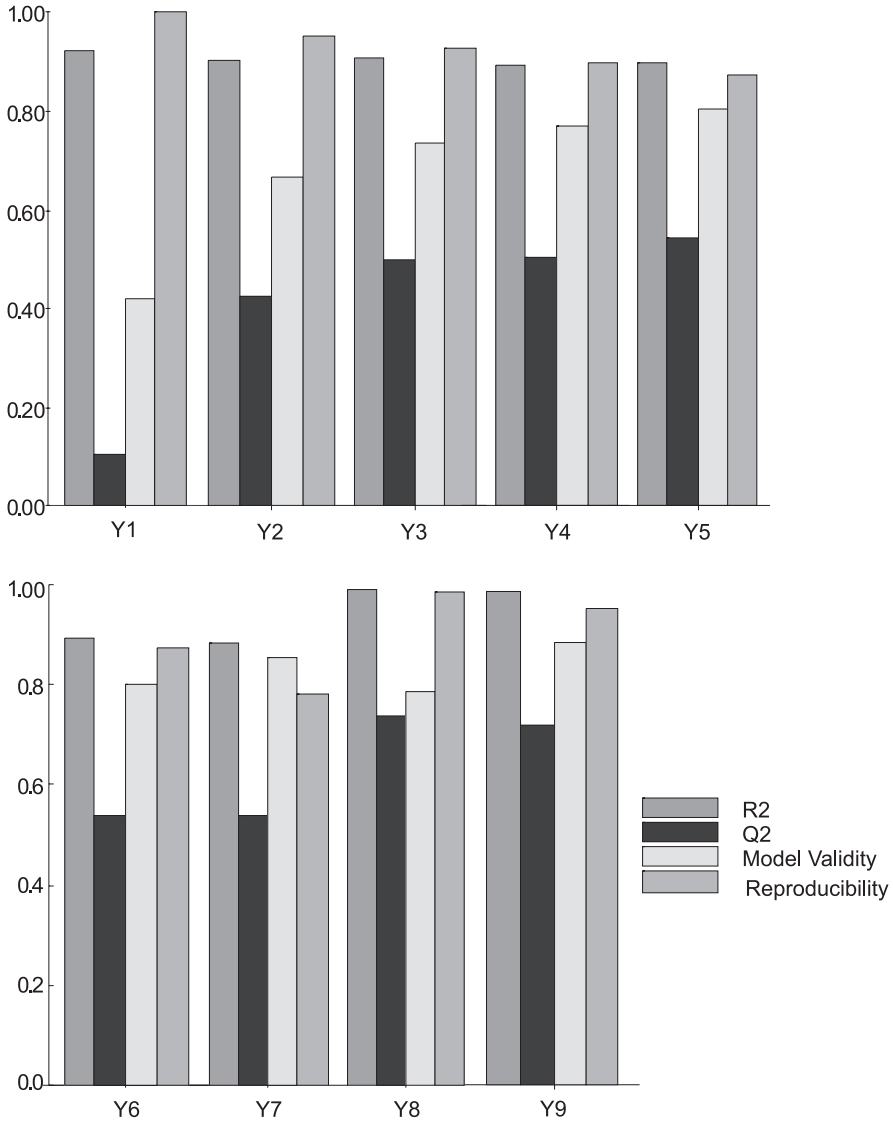

Figure 2. Summary of fit for the experimental design. Y_1 – Cumulative % carbamazepine released in 1 h; Y_2 – Cumulative % carbamazepine released in 2 h; Y_3 – Cumulative % carbamazepine released in 4 h; Y_4 – Cumulative % carbamazepine released in 6 h; Y_5 – Cumulative % carbamazepine released in 8 h; Y_6 – Cumulative % carbamazepine released in 10 h; Y_7 – Cumulative % carbamazepine released in 12 h; Y_8 – k Peppas; Y_9 – n Peppas

position (both qualitative and quantitative) of the tablets is presented in Table 6. The machine was regulated to obtain 350 mg weight and minimum 5 kgforce hardness 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 European Pharmacopoeia (16).

Determination of the dependent variables (the results)

Dissolution studies

The dissolution studies were performed with PharmaTest PT-DT7 device using the paddle method at a 100 rpm rotation speed (European Pharmacopoeia apparatus 1) and 1% aqueous solution of sodium lauryl sulfate as dissolution medium (16). Coated crystals (equivalents at 200 mg carba-

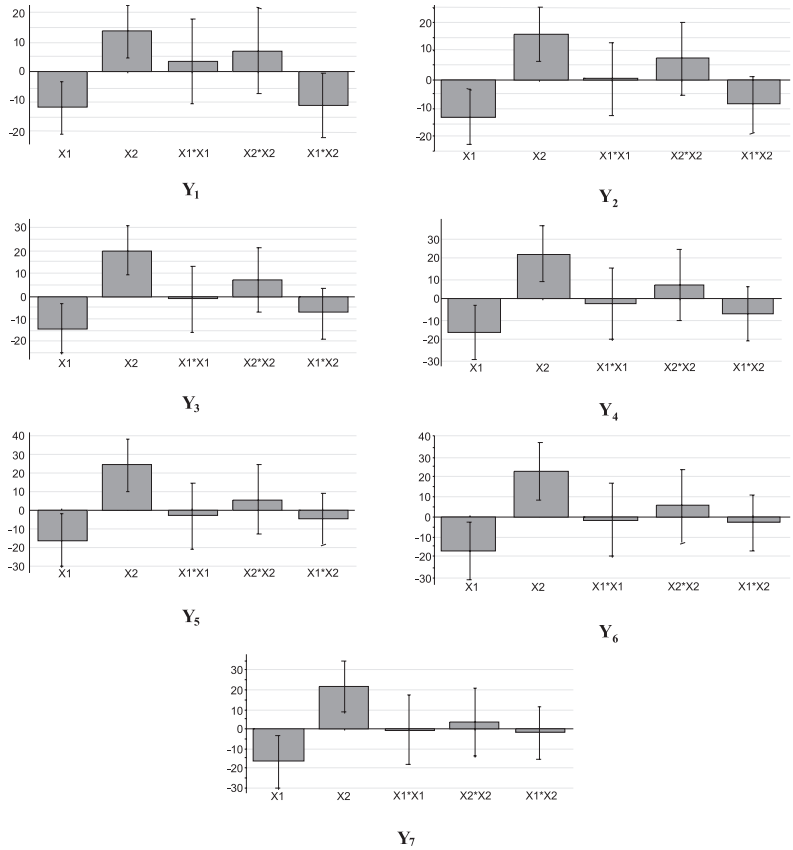

Figure 3. The influence of the formulation factors on the carbamazepine release at different dissolution time points (scaled and centered coefficients presentation). X_1 – Eudragit NE ratio; X_2 – HPMC ratio; Y_1 – Cumulative % carbamazepine released in 1 h; Y_2 – Cumulative % carbamazepine released in 2 h; Y_3 – Cumulative % carbamazepine released in 4 h; Y_4 – Cumulative % carbamazepine released in 6 h; Y_5 – Cumulative % carbamazepine released in 8 h; Y_6 – Cumulative % carbamazepine released in 10 h; Y_7 – Cumulative % carbamazepine released in 12 h

Table 7. Release models tested.

Baker-Lonsdale	$(3/2)\ [1 - (1 - (Q_t/Q_8)^{2/3}] - (Q_t/Q_8) = K_b t$
Peppas – Korsmeyer	$Q_t/Q_8 = K_p t^n$
Hixson-Crowell	$Q_0^{1/3} - Q_t^{1/3} = K_s t$
Higuchi	$Q_t/Q_8 = K_h t^{0.5}$
First order	$Q_t/Q_8 = K_1 t$
Zero order	$Q_t = Q_0 + K_0 t$

mazepine) were put into a dissolution vessel with 1000 mL dissolution medium. At specific time intervals, 2 mL samples of solutions were withdrawn, immediately filtered through a 0.45 µm filter and the drug concentration was assayed by HPLC with UV detection at 240 nm. Apparatus: HPLC Agilent 1100 series; chromatographic column: Zorbax SB-C18, 150 mm × 5.6 mm × 4.6 µm; mobile phase: acetonitrile : phosphoric acid 0.1% in water = 65:35 v/v; flow rate: 1.5 mL/min; retention time: 1.55 min. The initial volume of the vessel was maintained constant by adding 2 mL of fresh dissolution medium after each sampling. For each formulation, the dissolution studies were performed in triplicate.

Kinetic release evaluation

To evaluate the release profiles, several release models (Table 7) were tested such as Baker-Lonsdale (17), Korsmeyer-Peppas (18, 19), Hixson-

Crowell (20), Higuchi (21, 22) first order and zero order (23, 24). The mathematical models, shown in Table 7, were fitted to individual dissolution data with the regression module of Kinetica 4.4 for Windows. Regression analyses were used to obtain the release constant *k*, correlation coefficients *R* and Akaike Information Criterion (AIC) for each model. The Akaike criterion was chosen for distinguishing among competing models. In this criterion, a lower value of the indicator means a better fit. On the basis of the Akaike indicator we selected the mathematical model, which describes the release profile for all the analyzed samples with the greatest accuracy. The equation with the lowest value of the indicator was judged to be the most appropriate model for each system. The mechanism of drug release was analyzed using Peppas equation in which *k* is the release rate constant and *n* is the release exponent indicating the mechanism of drug release (18).

Stability testing

The film coated crystals (N5 and N8 formulation) were packed into a high-density polyethylene bottle. The bottles were placed inside the stability testing cabinet (Binder, Germany) pre-equilibrated to 20°C/60% RH (relative humidity). After 3 months (91 days) film coated crystals were tested for dissolution.

RESULTS AND DISCUSSIONS

Experimental design analysis. Goodness of fit

The matrix of the results is shown in Table 8. In order to fit the experimental data with the chosen experimental design and to calculate 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

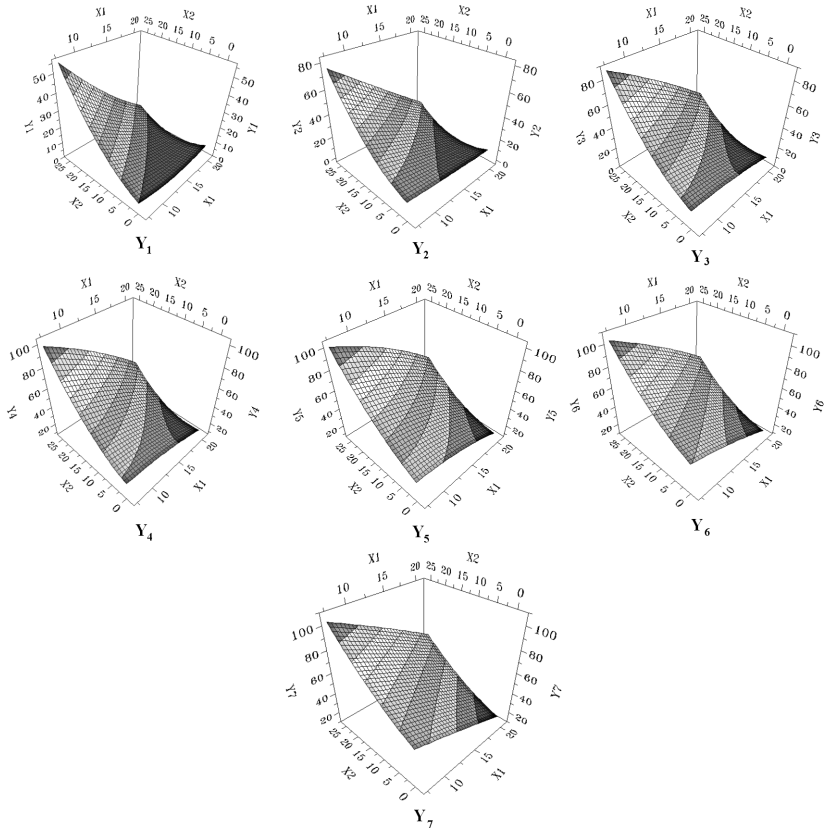

Figure 4. The influence of the formulation factors on the carbamazepine release at different dissolution time points (contour plot surface presentation). X_1 – Eudragit NE ratio; X_2 – HPMC ratio; Y_1 – Cumulative % carbamazepine released in 1 h; Y_2 – Cumulative % carbamazepine released in 2 h; Y_3 – Cumulative % carbamazepine released in 4 h; Y_4 – Cumulative % carbamazepine released in 6 h; Y_5 – Cumulative % carbamazepine released in 8 h; Y_6 – Cumulative % carbamazepine released in 10 h; Y_7 – Cumulative % carbamazepine released in 12 h

Table 8. Matrix of the results.

Exp No.	Y_1	Y_2	Y_3	Y_4	Y_5	Y_6	Y_7	Y_8	Y_9
N1	12.05	21.56	28.95	36.04	40.1	50.78	55.67	13.06	0.58
N2	2.24	4.51	6.21	7.96	8.5	12.60	15.94	2.07	0.80
N3	62.43	82.14	90.34	100.15	99.2	100.26	100.28	65.17	0.25
N4	7.21	13.67	24.63	29.79	37.66	43.89	49.67	8.48	0.71
N5	14.49	23.01	34.07	44.53	55.25	62.40	68.63	14.54	0.63
N6	7.55	13.60	18.67	24.44	28.25	31.62	37.36	8.29	0.60
N7	1.33	5.34	7.21	10.17	12.2	14.62	18.66	2.33	0.82
N8	27.81	52.36	72.95	89.93	98.35	100.36	99.84	32.13	0.58
N9	10.63	16.29	23.45	27.22	33.2	37.43	40.34	11.05	0.52
N10	11.44	20.94	28.661	35.81	40.23	43.56	56.43	12.76	0.57
N11	12.32	22.69	32.81	40.68	48.95	52.98	59.60	14.55	0.57

Y_1 – Cumulative % carbamazepine released in 1 h; Y_2 – Cumulative % carbamazepine released in 2 h; Y_3 – Cumulative % carbamazepine released in 4 h; Y_4 – Cumulative % carbamazepine released in 6 h; Y_5 – Cumulative % carbamazepine released in 8 h; Y_6 – Cumulative % carbamazepine released in 10 h; Y_7 – Cumulative % carbamazepine released in 12 h; Y_8 – k Peppas; Y_9 – n Peppas.

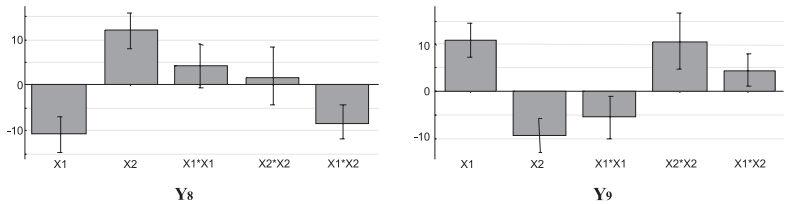

Figure 5. The influence of the formulation factors on Peppas equation kinetic release parameters (scaled and centered coefficients presentation). X_1 – Eudragit NE ratio; X_2 – HPMC ratio; Y_8 – k Peppas, Y_9 – n Peppas

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 indicating a very good model with excellent predictive power. R^2 and Q^2 provide the best summary of fitting the model (14).

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 well for Y_3–Y_9 responses and are satisfactory for Y_1, Y_2 responses.

ANOVA test (analysis of variance) shows if the variance of the results is determined by the modifications of the formulation factors or represents a variance determined by experimental errors (14). The results of ANOVA test have shown that the experimental data obtained for Y_1–Y_9 responses were good (p for model was lower than 0.05 and p for residual was higher than 0.05) for all responses (14).

Experimental design analysis. Formulation factor analysis

The results of *in vitro* release evaluation of the carbamazepine dissolved at different time intervals are shown in Figure 1 and Table 8.

The coefficients of the equation, used to fit the experimental data with the chosen model, represent the influence of studied factors and interaction between studied factors on the responses. The values of the coefficients (X_1, X_2) related to the effects of these variables on the corresponding responses (Y_1–Y_9). Coefficients with more than one factor term represent the interaction terms and coefficients with higher order terms are indicating the quadratic (non-linear) nature of the relationship. Two and three dimensional plots for the measured responses were formed, based on the model in order to assess the chance of the responses surface. Also, the relationship between the formulation factors (independent variable) and responses (dependent variables) can be further understood by these plots (14, 15).

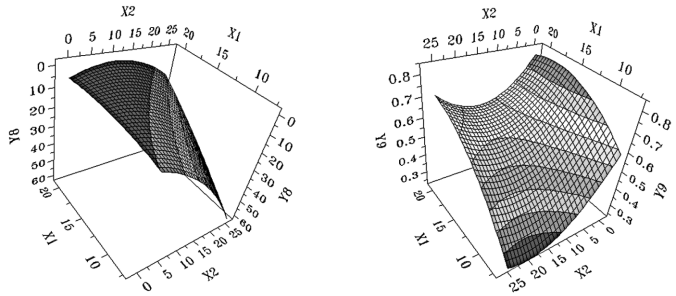

Figure 6. The influence of the formulation factors on Peppas equation kinetic release parameters (contour plot surface presentation). X_1 – Eudragit NE ratio; X_2 – HPMC ratio; Y_8 – k Peppas, Y_9 – n Peppas

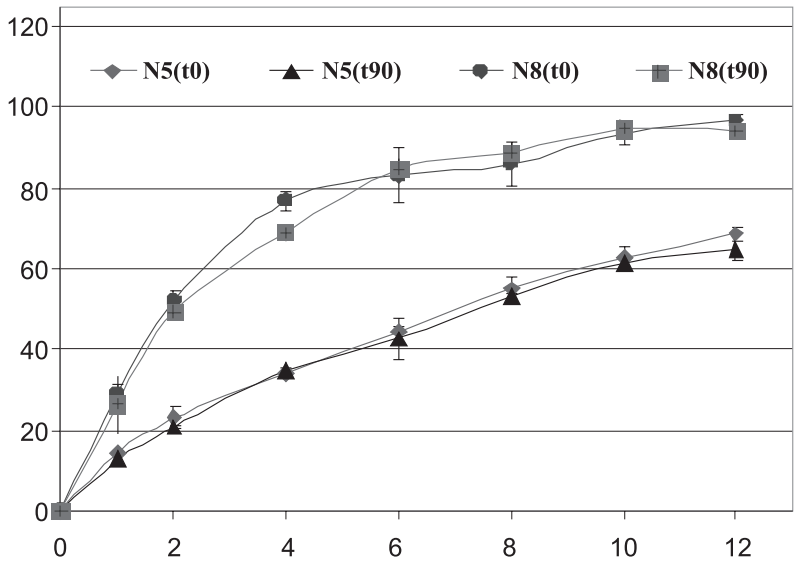

Figure 7. Dissolution profile of carbamazepine from coated cristals (N5 and N8 formulations) after the stabiliy testing under controled conditons (20°C/60%R)H. t0 – initial; t90 – 3 months.

The influence of the formulation factors on the responses is presented as scaled and centered coefficients in Figure 3 and as response surface plot in Figure 4. The results from the coefficients data analysis indicate the factor X_1 (Eudragit NE ratio) the most important factor on carbamazepine release, at all dissolution time points. By increasing the Eudragit NE ratio (polymer film forming ratio) a higher thickness polymeric coating film was produced and the amount of carbamazepine released at all the dissolution points was decreased (Figure 4). Similar results were found from pellets with diclofenac coated with Eudragit RS/RL (25) and with theophilline coated with Eudragit RS (26). The influence of the formulation factors X_1 on the release has approximately the same intensity at all dissolution points and the influence is almost linear in the experimental space (Figs. 3 and 4).

As expected, the second formulation factor X_2 (HPMC ratio) has a positive influence on carbamazepine release. By increasing the HPMC ratio (pores generating polymer) the drug release was increased at all the dissolution points. Similar results were found from pellets with metoclopramide hydrochloride coated with Surelease (10, 27). The intensity of the factor X_2 is smaller than the intensity of the factor X_1 (see Figure 3), and it is approximately linear in the experimental space (the coefficient of the equation term X_2*X_2 is very low, $p > 0.05$, and the quality of the model is enhanced, if these coefficients are discarded). The same conclusion results from the analysis of the response plot

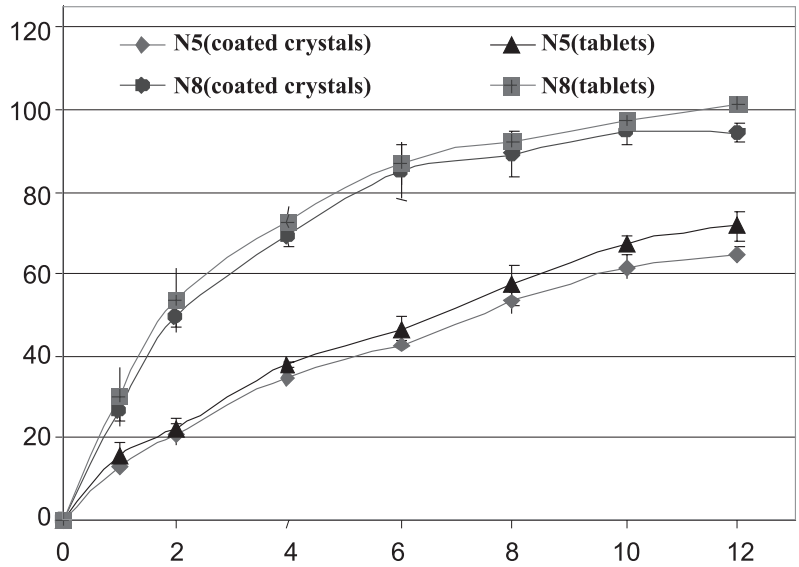

Figure 8. Dissolution profile of carbamazepine from coated cristals and tablets prepared with them (N5 and N8 formulations)

surface (Fig. 4). There are no interactions between the influences of the studied factors (the coefficient of the equation term X_1*X_2 is low, $p > 0.05$ and the quality of the model is enhanced, if these coefficients are discarded).

Kinetic release analysis

In order to study the kinetic release of carbamazepine from coated crystals, six well known kinetic release models were evaluated. Table 9 provides a summary of the model fitting and statistical parameters for kinetics release characterization of the prepared formulations N1–N10). The best fitting for the drug profile release, for all the experiments, (formulations N1–N10) was obtained with Peppas equation.

In order to analyze the influence of the formulation factors on kinetic release, the parameters of Peppas equation (k and n) were introduced in experimental design as responses ($Y_8 - k$ and $Y_9 - n$). The coefficients of the equation used to fit the experimental data with the chosen model at kinetic release evaluation are presented as scaled and centered coefficients in Figure 5 and as response plot surface in Figure 6.

The analysis of the coefficients equation has shown that both studied factors have an influence on Peppas equation parameters, k and n (Figs. 5 and 6). The influence of formulation factors on k parameter is similar with the influence of formulation factors on *in vitro* carbamazepine release at different dissolution time point intervals. First formulation factor (X_1 – Eudragit ratio) has a negative influence on k parameter of the Peppas equation, increasing the amount of film coating polymer (the increase of Eudragit NE ratio), increased polymer film thickness, and decreased the release rates of carbamazepine and also, the value of k parameter, respectively. The intensity of the influence is approximately linear in the experimental space (the coefficient of the equation term X_1*X_1 is very low, $p > 0.05$, $p > 0.05$, and the quality of the model is enhanced, if these coefficients are discarded). The second studied formulation factor (X_2 – HPMC ratio) has positive influence on k parameter and on drug release, respectively. By increasing the HPMC ratio (the amount of pores forming polymers ratio) in the coated film, the release rates of carbamazepine and the value of k parameter was increased. The influence of the formulation factor X_2 is similar as intensity with the influence of the formulation factor X_1 (the values of centered and scaled coefficients are approximately the same). On the other hand, there is a strong interaction between the influence of formulation factor X_1 and the influence of formulation factor X_2 (interaction X_1*X_2); at high level of Eudragit ratio (more than 15%) the increase of HPMC ratio between 0–12% has no effect on drug release and has a very low release effect. This behavior can be explained; at a high thickness film

Table 9. Results of the kinetic release characterization.

	Baker and Lonsdale			Peppas				Hixon and Crowell		
	R	AIC*	K	R	AIC*	k	n	R	AIC*	k
N1	0.978	26.62	0.0051	0.999	15.58	13.06	0.584	0.942	32.42	0.022
N2	0.957	18.59	0.0003	0.994	8.88	2.07	0.802	0.987	11.48	0.005
N3	0.995	14.32	0.0905	0.997	14.13	65.17	0.251	0.985	16.89	0.250
N4	0.968	31.18	0.0034	0.999	14.42	8.48	0.713	0.990	24.26	0.018
N5	0.975	32.45	0.0078	1.000	6.58	14.54	0.627	0.985	30.05	0.029
N6	0.988	20.97	0.0019	0.998	12.05	8.29	0.597	0.958	28.67	0.013
N7	0.951	21.65	0.0004	0.993	11.83	2.33	0.824	0.988	13.03	0.006
N8	0.977	23.70	0.0333	0.996	12.68	32.13	0.583	0.995	17.52	0.096
N9	0.996	14.41	0.0026	0.999	8.41	11.05	0.523	0.931	32.66	0.015
N10	0.982	28.00	0.0045	0.992	25.33	12.76	0.574	0.954	33.70	0.021
N11	0.989	26.53	0.0059	0.999	16.29	14.55	0.568	0.964	33.52	0.025
TG*	0.980	32.60	0.011	1.000	4.60	17.53	0.622	0.988	29.26	0.038
	Higuchi			First order			Zero order			
	R	AIC*	k	R	AIC*	k	R	AIC*	k	
N1	0.990	21.77	15.49	0.961	30.19	0.075	0.884	36.38	5.19	
N2	0.960	18.18	3.87	0.988	11.12	0.014	0.985	12.26	1.33	
N3	0.963	19.71	51.33	0.994	14.24	0.902	0.730	25.27	28.01	
N4	0.978	29.03	13.13	0.994	20.47	0.060	0.975	29.67	4.47	
N5	0.991	27.24	18.84	0.993	25.66	0.101	0.952	37.11	6.35	
N6	0.993	18.03	10.10	0.966	27.45	0.042	0.939	30.87	3.39	
N7	0.955	21.21	4.55	0.990	12.53	0.017	0.986	14.10	1.57	
N8	0.993	19.17	36.00	0.998	13.44	0.350	0.937	27.74	16.91	
N9	0.999	8.58	11.58	0.944	31.46	0.050	0.900	34.81	3.85	
N10	0.988	25.41	14.83	0.965	32.08	0.070	0.924	36.68	4.96	
N11	0.996	20.94	16.68	0.978	30.72	0.084	0.924	37.99	5.57	
TG**	0.992	26.77	22.00	0.995	23.92	0.134	0.953	37.55	8.15	

* Akaike Information Criterion. **TG – Tegretol CR 200 mg, controlled release tablets

Table 10. Profile release comparison – stability study.

Profile comparison	f_2
N5 (t_0) – N5 (3 months)	85.62
N8 (t_0) – N8 (3 months)	66.97

Table 11. Profile release comparison – evaluation of the integrity of the coated carbamazepine crystals during tabletting process.

Profile comparison	f_2
N5 (coated crystals) – N5 (tablets)	70.54
N8 (coated crystals) – N8 (tablets)	71.39

Table 12. The optimum formula – level of formulation factors.

Formulation variabiles	Symbol	Value
Eudragit NE ratio	X_1	17.17
HPMC ratio	X_2	22.51

Table 13. The optimum formula – results.

Responses		Theoretical (Predicted)	Practical (Obtained)
Cumulative % carbamazepine released in 1 h	Y_1	16	16.25
Cumulative % carbamazepine released in 2 h	Y_2	29	27.33
Cumulative % carbamazepine released in 4 h	Y_3	43	40.90
Cumulative % carbamazepine released in 6 h	Y_4	52	55.24
Cumulative % carbamazepine released in 8 h	Y_5	60	63.80
Cumulative % carbamazepine released in 10 h	Y_6	63	68.25
Cumulative % carbamazepine released in 12 h	Y_7	66	73.02
k – Peppas	Y_8	17.54	18.16
n – Peppas	Y_9	0.61	0.59

coating polymer, Eudragit NE needs minimum 10% HPMC in the composition of the film coating polymers to act as pores forming.

Regarding the influence of the formulation factors on *n* parameter from Peppas equation, the increase of the film coating polymer (Eudragit NE 40D) amount, conducts to the increase of *n* value and to a system with 0 order release kinetics (Fig. 5). The zero order release behavior here may suggest that the release of carbamazepine was controlled by the constant diffusion of the drug *via* film coating polymer. The second studied formulation factor (X_2 – HPMC ratio) has a negative influence on *n* parameter. The increase of the pores forming polymer ratio (HPMC ratio) decreases the value of *n* and leadsd to a system with Higuchi kinetic release behavior (*n* value close to 0.5) (see, Fig. 5). The Higuchi kinetic release behavior here may suggest that the release of carbamazepine from this type of system was controlled by diffusion and erosion: diffusion of the drug *via* polymeric film and probable erosion of the HPMC from coating film and during pores forming. The influence of the pores forming polymer ratio (HPMC ratio) on *n* parameter from Peppas equation is not linear in the experimental space (the coefficient of the equation term X_2*X_2 is high, – see, Figure 5), and presents a curvature between 16–22% HPMC ratio (see, Fig. 6).

Stability study

Two formulations, one with dissolution release profile on 12 h (formulation N5) and one with dissolution profile on 24 h (formulation N8) were selected as formulations for further investigations (stability study and tablets preparation). Formulations N5 and N8 were placed on stability study. After 3 months, the formulations were reevaluated from the point of view of the dissolution release profile. The dissolution profiles of the formulation from stability study are illustrated in Figure 7. In order to evaluate similarity between the dissolution profiles performed immediately after preparation with the dissolution profile obtained after three months storage, similarity factor f_2 was used (28). The f_2 (similarity factor) is inversely proportional to the average squared difference between the two profiles, with emphasis on the larger difference among all the time points. The use of this factor was recommended for dissolution profile comparison in the FDA's guides for industry (29–31). According to these guides, generally, f_2 values higher than 50 (50–100) ensure sameness or equivalence of the two curves. No significant differences on dissolution profiles were observed, the value of similarity factors f_2 begin higher than 50 in both cases (Table 10). This means, no changes in drug release were detected after 3 months of storage under ambient conditions (20°C; 60%RH) for carbamazepine crystals coated with Eudragit NE. These results lead to the conclusion that a curing treatment consisting in drying the coated crystals for 30 min at 40°C performed in the fluid bed system at the end of coating process is enough to obtain a coating film with good coalescence, which won't change the dissolution rates during storage.

Evaluation of compressed coated carbamazepine crystals

The same formulations (N5 and N8) used in stability studies were compressed in order to evaluate the integrity of the coated carbamazepine crystals during tabletting process. In order to avoid coat-

ing film destruction, there are necessary a high amount of excipients with plastic properties as microcrystalline cellulose (32). The composition (both qualitative and quantitative) of the tablets is presented in Table 6. The obtained tablets have very good pharmacotechnical properties: disintegration time max. 2 minutes; resistance to crushing 6–7 kg; friability lower than 0.3%; good mass uniformity. Figure 8 shows the carbamazepine release from uncompressed coated carbamazepine crystals and compressed coated carbamazepine crystals into tablets. In order to evaluate the similarities between the dissolution profiles obtained on uncompressed coated carbamazepine crystals with the dissolution profile obtained on coated carbamazepine crystals into tablets, similarity factor f_2 was used (28). No significant differences on dissolution profiles were observed, value of similarity factors f_2 was higher than 50 (Table 11). According to the obtained *in vitro* dissolution data, the integrity of the coating film was preserved after the compression of the coated carbamazepine crystals into tablets. Similar results were found from pellets coated with Eudragit RS 30D/RL (32–34), Eudragit NE30D (35) or pellets coated with Kollicoat RS 30D (36).

Optimum formula determination

In order to obtain a controled release dosage form with drug release over 12 h, the experimental formulation should be compared with the dissolution profile of TEGRETOL CR 200, selected as reference dosage form. The release profile of TEGRETOL CR 200 was analyzed and the release kinetics was also described by Peppas equation.

Using the optimization module from Modde 6.0 software and the desired value for the response Y_8 and Y_9, the values k and n value of Peppas equation obtained on TEGRETOL CR 200, the optimum formula was calculated. The level of the formulation factor for the optimum formula is shown in Table 12. The optimum formula was performed and analyzed in the same conditions as experimental formulation. The obtained results of the optimum formula are shown in Table 13. The experimental values obtained for the optimum formula were close to the theoretical results predicted by the experimental design (Table 13). These results validated the experimental design and the conclusion resulted from the experimental design analysis and interpretation.

CONCLUSIONS

In this works it was developed and optimized a technology to obtain multiparticulate extended release pharmaceutical dosage forms with carbamazepine by coating directly carbamazepine crystals (fraction 250–600 μm) with an insoluble but permeable polymer (Eudragit NE) in a fluid bed coating system. The best characterization of *in vitro* kinetic release profile can be performed using Peppas equation. It is possible to modulate the desired kinetics release of carbamazepine from the extended release dosage form by modifying the thickness of the film coating and the amount of pores forming polymer in the coating film.

By using an experimental design in which the independent variables (the formulation factors) are the amount of polymer film forming and the pores forming polymer ratio, and the dependent variables (responses) the k and n parameters from Peppas kinetic release equation, it is relatively easy to modulate the desired kinetic release of carbamazepine and to obtain multiparticulate extended release pharmaceutical dosage forms with carbamazepine for 12 or 24 h release time.

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