Research Article

Development of Different Polymer Matrix Systems for Galantamine Hydrobromide Sustained Release

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ABSTRACT

This paper outlines the development of controlled release matrix systems containing galantamine hydrobromide. The model compositions were developed by the direct compression technique, using a variety of hydrophilic and hydrophobic polymer carriers: Methocel® K100LV, Methocel® K4M, Kollidon® VA64 and Kollidon® SR at different concentrations. The swelling and erosion rate, as well as in vitro drugrelease characteristics of the studied matrices were investigated. Various mathematical models were used in order to evaluate the in vitro release kinetics and mechanism of galantamine hydrobromide. It was found out that the increase of the polymer quantity leads to change in the drug release mechanism from Fickian diffusion to Anomalous (non-Fickian) diffusion.

Keywords: galantamine hydrobromide, drug delivery systems, sustained drug release, matrix tablets.

INTRODUCTION

Alzheimer's disease (AD) is a progressive neuro degenerative disorder that accounts for most common cause of degenerative dementia in the population age over 65 and is also a common cause of dementia in those under 65.[1,2] It is characterized by progressive loss of memory and cognition, ultimately leading to complete debilitation and death. The number of the disease is estimated to reach over 100 million worldwide by the year 2050, therefore this is a growing public health concern with major socio economic significance.[3]

An improvement in cognitive and behavioral symptoms of the activity in the treatment of mild to moderate dementia in people with Alzheimer's disease, is observed using galantamine hydrobromide at a dose of 16-24 mg per day.[4-6] Galantamine hydrobromide belongs to the group of choline sterase inhibitors. It is a reversible, competitive inhibitor of the enzyme acetyl choline sterase.[7] Galantamine hydrobromide is a weak base with a pKa = 8.2, sparingly soluble in water (31 mg/ml) and very slightly soluble in anhydrous alcohol. It is rapidly and completely absorbed (90% oral bioavailability) after oral administration, and the time necessary to reach the maximum plasma concentration (t_{max}) is approximately 1 hour.[8]

According to the Biopharmaceutics Classification System (BCS), galantamine belongs to class I - drugs with high solubility and high permeability.[9]

The efficiency of the drug therapy can be optimized by controlling the rate and extent of its release in the body. One of the most commonly used methods of developing controlled release formulations for therapeutic agents is to include them in matrix tablets. Such type of systems can be easily manufactured by direct compression with conventional tableting facilities and their modification involves few processing variables[10], and varying different types of polymer carriers.[11]

Undoubtedly, the most widely used hydrophilic polymer matrix carrier is Hydroxypropyl methylcellulose (HPMC). One of the main reasons is the peculiarity to swell that could enable to control drug release. Upon contact with water or biological fluids, the outer layer of HPMC polymer matrix is hydrated, which leads to the transformation of the polymer from the glassy to rubbery state, which causes the polymer to swell. This generates a pseudo-gel layer around the tablet core which controls the drug release from the inner to the outer side of the tablets and the rate of water diffusion within the matrix. The release mechanisms depend on the drug solubility and the swelling and erosion properties of the polymer. The release mechanism of soluble drug substances occurs primarily by diffusion with a limited matrix erosion share and anomalous diffusion due to relaxation of polymer macromolecular chains.[12]

Representative of the group of water-soluble polymersis a vinyl pyrrolidone-vinyl acetate copolymer with trade name Kollidon® VA64. It is water soluble copolymer with molecular weight of 45,000–70,000, which contains the two monomers in ratio of 6:4. Copovidone has an excellent binder activity as a dry binder in direct tableting in concentration between 5 and 15%.[13] It can be used also as a matrix agent.[14]

Typical matrix former polymer belonging to the group of hydrophobic carriers often used in the tablet industry is polyvinyl acetate/povidone based Kollidon® SR. It is a free-flowing, non hygroscopic powder, consisting of polyvinyl acetate (80%, w/w) and polyvinyl pyrrolidone (20%, w/w) combined as a physical mixture. Approximately 0.8% sodium lauryl sulphate and 0.2% silica are used as stabilizers.[15] It possesses excellent flowability and is often used as an excipient for direct

compression. The tablets are characterized by low friability and high mechanical strength at low compression forces during the tableting process.[16] Kollidon® SR has a unique character of maintaining the tablet geometric shape until the end of dissolution test.This is mainly due to its major component - the water insoluble polyvinyl acetate, while the minor water soluble part- polyvinyl pyrrolidone, is responsible for pore formation causing diffusion controlled release mechanism.[17]

The aim of this research was to develop matrix systems containing galantamine hydrobromide by using Methocel® K100LV, Methocel® K4M and Kollidon® SR as release controlling polymers and Kollidon® VA64 as polymer which increases the retarding effect of the system. Moreover, we aimed to investigate the influence of the quantity and the type of the polymeric carrier on the technological and biopharmaceutical parameters of different model compositions and to determine the mechanism of drug release from the obtained systems.

MATERIALS AND METHODS

Materials

Galantamine Hydrobromide (Sopharma PLC, Bulgaria), Hypromellose, nominal viscosity 100 mPa·s (Methocel® K100LV Premium CR - Dow Chemical Co., USA), Hypromellose, nominal viscosity 4000 mPa·s (Methocel® K4M Premium CR - Dow Chemical Co., USA), Polyvinyl acetate and povidone based matrix retarding agent (Kollidon® SR, BASF SE, Germany), Copovidone (Kollidon® VA64, BASF SE, Germany), Lactose monohydrate (Tablettose® 70 – Meggle, Germany), Magnesium stearate (Magnesia, Germany) and Silica, colloidal anhydrous (Aerosil® 200 – Evonik, Germany).

Methods

Preparation of Model Matrix Systems

The model matrix systemscontained 30.77 mg galantamine hydrobromide (equivalent to 24.0 mg galantamine base), different quantities of matrix polymers and other functional excipients. All systems were prepared by the method of direct compression. Tabletting was carried out on a rotary tablet press (Fette 52i), provided with compression tools, which were designed to produce round biconvex tablets with a diameter of 9 mm. All samples were prepared under the same parameters of the tabletting press, pre-compression force 2-3 kN, main-compression force 10-12 KN, “dwell time” 50-55 ms.

Factorial Design

The mathematical model for a two-factor (*a* x *b*) design is:

$$y_{ijk} = \mu + \alpha_i + \beta_j + \alpha\beta_{ij} + \varepsilon_{ijk}, \quad (1)$$

where μ is the overall mean for all experiments; α_i is the effect of the i^{th} level of factor *a;* β_j is the effect of the j^{th} level of factor *b;* $\alpha\beta_{ij}$ is the interaction effect between the i^{th} level of factor *a* and j^{th} level of factor *b*, and ε_{ijk} is a random effect due to sampling.[18]

Response Surface Methodology

Response Surface Methodology (RMS) is useful for the modeling and analysis of problems in which a response of interest is influenced by several variables and the objective is to optimize this response. The mathematical model for a two factor (*a* x *b*) design is:

$$E(y) = f(x_1, x_2), \quad (2)$$

where E(y) is the expected value of the response, and x_1, x_2 are the levels of the two factors.[19] The response surface is represented graphically as a surface plot in three-dimensional space. Several contours of the response surface are plotted for depicting the shape of a response surface. Each contour corresponds to a particular height of the response surface. The contour plot is helpful for studying the levels of the two variable factors that result in changes in the shape or height of the response surface.

Investigation on Swelling and Erosion Kinetics of the Matrix Tablets

The test was performed by using the method described by Reynold.[20] The tablets were accurately weighed and immersed in 50 ml PBS (pH 6.8), at 37 ˚C. The tablets were taken out in predefined intervals (up to 18 hours). Water from the surface was carefully removed by blotting with filter paper and the weight was measured. The tablets were dried to a constant weight for a period of 48 h, at 50 ˚C in a vacuum oven. The swelling of matrix tablets and their erosion, average of six tablets, were calculated by using the next equations:

$$Swelling(\%) = \frac{(W_s - W_d)}{W_d} \times 100, \quad (3)$$

where W_s and W_d are the weights of the swollen tablets and tablets after drying respectively.

$$Erosion(\%) = \frac{(W_t - W_d)}{W_t} / \times 100, \quad (4)$$

where W_t is the initial mass of the tablet.

In Vitro Drug Release Studies

The test was performed by using apparatus 2 – paddle dissolution test, according to USP - SOTAX AT 7 (Switzerland). The test was carried out at a paddle rotation speed 50 ± 2 rpm, maintained at 37 ± 0.5˚ C, in 500 ml aqueous medium at: (i) pH 6,8 (PBS) and (ii) change of pH conditions – the tablets were immersed in 0.1 M HCl solution (pH 1.2) for 2 hours and then the pH of dissolution media was changed to 6.8 (PBS). Samples of 5 ml were withdrawn at preselected intervals up to 8 hours and replaced with 5 ml of fresh media. Each sample was filtered through a 0.45 µm membrane filter (Sartorius cellulose acetate filter, Germany). The amount of the drug released was determined by UV absorbance at 288 ± 2 nm using Hewlett-Packard 8452 A Diode Array

spectrophotometer (New Jersey, USA). The cumulative percentage of drug release was calculated and the average of six determinations was used in data analysis.

Drug Release Kinetic Study

The mechanism of drug release from the formulations was predicted by fitting data of drug release to different kinetic models:

Zero order kinetic: $M_t = k_0 t$ (5)

First order kinetic: $M_t = M_0 \cdot e^{-k_1 t}$ (6)

Square root model:[21] $M_t = k_2 \sqrt{t}$ (7)

Korsmeyer-Peppas model:[22] $M_t / M_\infty = kt^n$ (8)

where: M_t is the amount of drug release at time t; M_0– initial amount of drug in the matrix tablets; M_t/M_∞ is the fraction of drug released at time t; k_o, k_1, k_2 are the release constants; k is a constant incorporating the structural and geometric characteristics of the drug dosage form and n is the release exponent.

Determination of Similarity Factor (f_2)

Similarity factor was used for comparison of dissolution profiles of matrix tablets.[23] It was calculated by the equation:

$$f_2 = 50\log\{[1 + (\tfrac{1}{n})\textstyle\sum_{i=0}^{n}(R_i - T_i)^2]^{-0.5} \times 100\}, \quad (9)$$

where: n is the number of time points for each of the studied dissolution curves, R_i and T_i is the cumulative dissolved drug for reference and product respectively.

RESULTS AND DISCUSSION

Preparation of model matrix systems

The composition of model matrices (M1-M10) is presented in table 1. ModelsM1-M4 were based on a combination of Methocel® K100LV and Kollidon® VA64 in different ratios. The systems M5-M7 were Methocel® K4M based (amounts of 25.0%, 37.5% and 50.0% of a tablet weight), and M8-M10 were Kollidon® SR based (amounts of 25.0%, 31.25% and 37.5% of a tablet weight).

The model tablets also contained Tablettose® 70 as a filler, magnesium stearate as a lubricant and Aerosil® 200 as a glidant. The total weight of the tablets was 300.0 mg.

The technological properties of the produced model matrices (Models M1-M10) are given in Table 2.

The data presented in Table 2 indicate that all formulations meted the requirements of the Ph. Eur. 7.0 for uniformity of mass and uniformity of dosage units. A well expressed increase of the mechanical strength of the tablets was observed in the models M2 and M4, in comparison with the models M1 and M3. This was due to the increase in the amount of the binding agent Kollidon® VA64 from 9 to 45 mg. The friability results of not more than 1.0 % (according to Ph. Eur. 7.0., chapter 2.9.7. requirements), were expected by the mechanical strength of the tablets. The acceptance value (AV) was limited to not more 15.0 according to the Ph. Eur. 7.0., chapter 2.9.40., test for content uniformity. As it is shown in table 2, all AV's were very low, which could be assumed as an equal drug distribution among the tablet mixtures and respectively a good uniformity of drug content for all models.

Investigation on Swelling and Erosion Kinetics of the Model Matrix Tablets

All model formulations were investigated for swelling and erosion extent of the matrices. The results are presented in Figure 1.

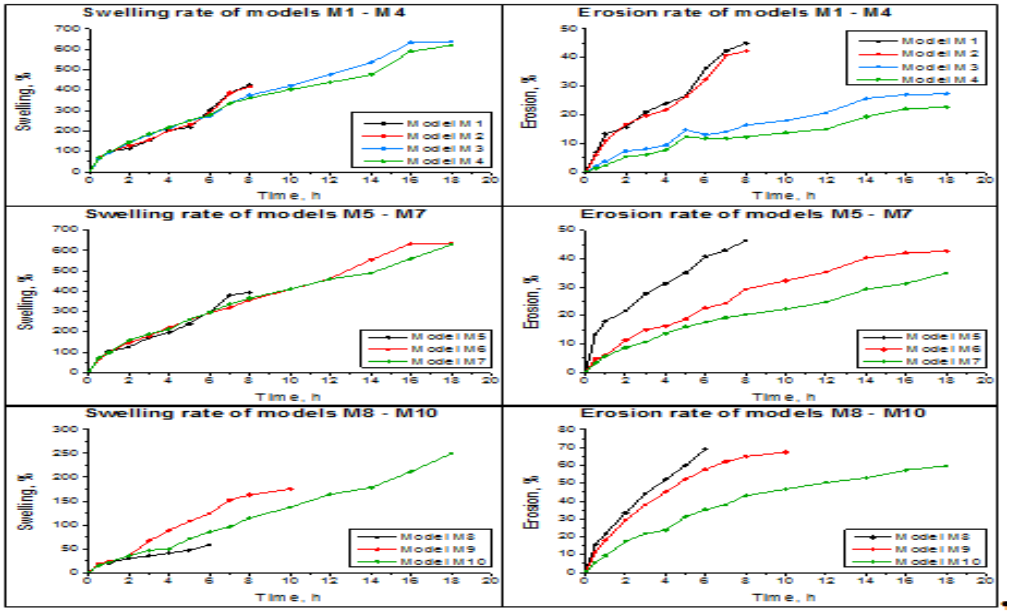

Figure 1: Swelling and erosion kinetics of models: M1-M4 (top), M5-M7 (middle) and M8-M10 (bottom)

The study results showed varying degrees of swelling and erosion rate depending on the polymer carrier type and its quantity. At low HPMC tablet content of 25%, regardless of the type of polymer - Methocel® K100LV (models M1 and M2, Figure 1) or Methocel® K4M (model M5, Figure 1), a rapid reaching of an swelling equilibrium of about 400% for 8 hours was observed. Due to the fact that the concentration of the matrix polymer is critical to the rapid formation of a gel layer, which prevents wetting of the interior and disintegration of tablet core, it may be reasonably, that it was observed a strong erosion for all three models (M1, M2 and M5), more than 45% for 8 hours. On the other hand, it was considered that the hydrophilic filler Tablettose® 70 had substantial influence on the increased erosion rate. It was expected that soluble excipients may affect polymer erosion, since there was competition for water between the additives and the polymer. The lower polymer concentrations in the matrix tablets produce gel layers of lower viscosity with fewer polymer-polymer entanglements.[24]

The various content of the binding agent Kollidon® VA64 at the models M1 and M2 did not have statistical impact on the swelling and erosion rate of the matrix tablets. With increasing of the matrix carrier HPMC concentration at 50%, the swelling rate of the models M3, M4 and M7 for 8 hours was comparable to the models M1, M2 and M5, but the equilibrium swelling was reached for 18 hours, and it was about 600%. At the same time, the erosion rate was delayed and it was in the range of 15-20% until the 8th hour.

Table 1: Compositions of the Matrix Systems

Ingredient	Model									
	M1 [mg]	M2 [mg]	M3 [mg]	M4 [mg]	M5 [mg]	M6 [mg]	M7 [mg]	M8 [mg]	M9 [mg]	M10 [mg]
Galantamine. HBr	30.77	30.77	30.77	30.77	30.77	30.77	30.77	30.77	30.77	30.77
Tablettose® 70	173.23	143.23	98.23	68.23	188.23	150.73	113.23	188.23	169.48	150.73
Methocel® K100LV	75.0	75.0	150.0	150.0	-	-	-	-	-	-
Kollidon® VA64	15.0	45.0	15.0	45.0	-	-	-	-	-	-
Methocel® K4M	-	-	-	-	75.0	112.5	150.0	-	-	-
Kollidon® SR	-	-	-	-	-	-	-	75.0	93.75	112.5
Aerosil® 200	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0
Magnesiumstearate	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0

Table2: Technological Parameters of the Matrix Tablets

Model	Mechanical strength		Uniformity of Mass		Friability, %	Uniformity of Dosage units, AV
	Average strength, N	% RSD	Average weight, g	% RSD		
M1	99.1	11.10	0.302	1.56	0.18	4.4
M2	170.8	8.90	0.301	1.37	0.18	3.5
M3	184.6	12.17	0.299	1.85	0.12	3.4
M4	263.3	11.95	0.300	1.54	0.09	4.2
M5	94.5	5.40	0.301	0.75	0.23	3.8
M6	99.2	4.72	0.301	0.62	0.22	3.5
M7	106.1	9.08	0.300	1.13	0.13	2.8
M8	96.6	12.23	0.301	1.62	0.35	3.5
M9	101.3	11.84	0.299	1.75	0.19	3.1
M10	105.7	12.92	0.298	1.89	0.03	3.3

Table 3: Drug Release Kinetic Study

Model	Zero order	First order	Square root model	Korsmeyer-Peppas model		T_{50} [min]
	R	*R*	*R*	*R*	*n*	
M1	0.926	- 0.979	0.995	0.997	0.43	119
M2	0.950	- 0.949	0.999	0.999	0.48	149
M3	0.967	- 0.927	0.996	0.996	0.64	214
M4	0.973	- 0.980	0.995	0.997	0.67	220
M5	0.909	- 0.947	0.988	0.991	0.42	174
M6	0.954	- 0.938	0.999	0.998	0.50	179
M7	0.961	- 0.989	0.997	0.996	0.58	238
M8	0.909	- 0.997	0.988	0.985	0.45	112
M9	0.945	- 0.982	0.996	0.992	0.53	149
M10	0.923	- 0.981	0.983	0.967	0.64	292

At the models based on Kollidon® SR (M8-M10, Figure 1) significantly lower degree of swelling was observed in comparison to the HPMC based compositions.

It was only 70% for model M8 at the 6th hour, while at the same time model M10 demonstrated a swelling rate of about 85% and the swelling equilibrium of 250% was reached for18 hours.

It was a logical result taking into consideration that HPMC polymers are water soluble, where as Kollidon® SR is water insoluble matrix polymer. The concentration is especially critical for the degree of erosion of the water insoluble matrix polymer.

It was observed up to 70% erosion for 6 hours at the model M8, which contains 25% Kollidon® SR.

After that the tablets disintegrated completely.

The erosion considerably slows down with an increase of the carrier matrix content as for the models M9 and M10 it was about 55% and 35% at 6th hour, respectively.

In Vitro Galanthamine hydrobromide Release Study

In order to determine the conditions of *in vitro* determination, the tests of models M2, M5 and M8 were performed in two different pH medium: (i) in pH 6.8 and (ii) in changed pH medium. The results presented in Figure 2 show that the release of galantamine hydrobromide from the models was pH independent, which was confirmed by calculations of similarity factor f_2=73.1 (model M2), f_2=81.5 (model M5), f_2=79.7 (model M8). Based on these results, further tests were performed in dissolution medium with pH 6.8.

The galantamine hydrobromide release profiles of models M1-M10 in dissolution medium pH 6.8 are presented in Figure 3.

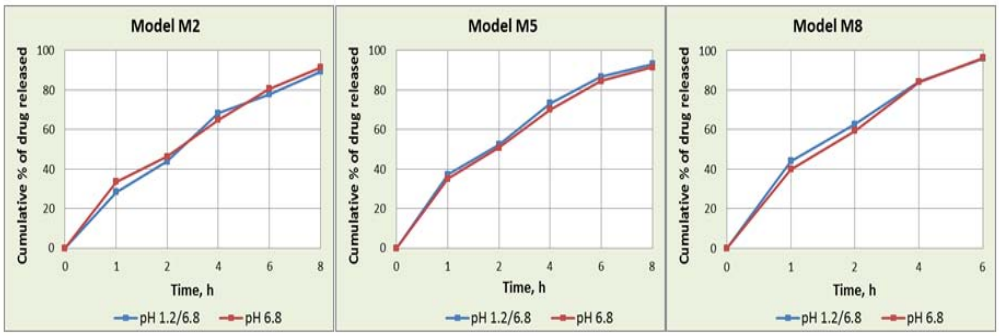

Figure 2: A comparative dissolution profiles of the models M2, M5 and M8 in a dissolution medium with pH 6.8 and in changed pH medium.

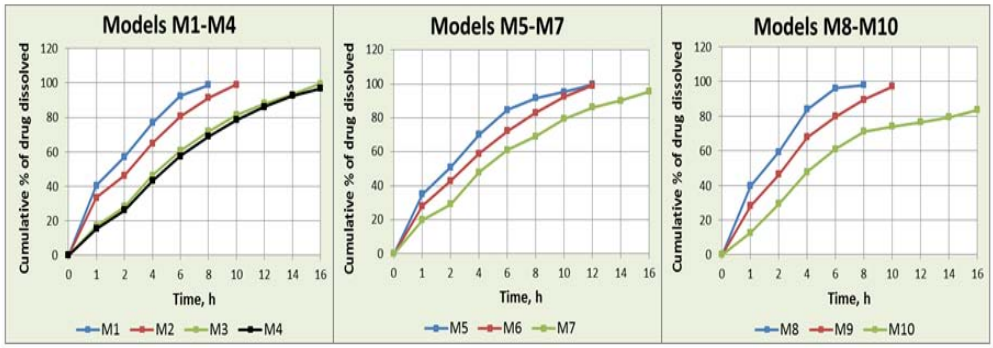

Figure 3: Release profiles of galantamine hydrobromide from the matrix tablets in dissolution medium with pH 6.8.

The results showed that both the degree and rate of drug release depended on the type of the matrix polymer and its quantity in the model formulations. Systems with low polymer concentrations up to 25% (model M1, M2, M5 and M8) showed fast galantamine hydrobromide release. At model M8, based on Kollidon® SR, 100% of the drug was released until the 6th hour, which was logical considering the erosion data of this model. Among the systems with polymer concentrations of 25%, best retarding properties were observed with the both models, which were basedof HPMC. In models M2 and M5, 95% of drug release was reached for 8 hours. By increasing of the HPMC content in the tablets, the release process was more prolonged in agreement with the swelling and erosion kinetics data. Both models M3 and M4, based on Methocel® K100LV, which contain 50% matrix polymer demonstrated an analogous drug release rate of about 70% galantamine hydrobromide until the 8th hour. Similar release profile provided a model M7, which also contains 50% Methocel® K4M in a tablet. It should be noted that the drug release rate was close, despite of the difference in molecular weight of the two polymer carriers. This was in concordance with the results of swelling and erosion kinetics of both polymers, which give similar values. This was most likely due to the inclusion of the binder Kollidon® VA64 in the tablets, based on

Methocel® K100LV. It contributes to more robust structure of the tablets systems, which was confirmed from the mechanical strength data (Table 2). The model M4 demonstrated a mechanical strength higher than the model M7, at the same polymer quantity and the same conditions of tableting. Especially valuable release profile showed model M6. Until the 2nd hour, it released 41% of the included drug substance, until the 4th hour it released 60%, and for 8 hours over 80%. Typical of matrix tablets based HPMC is their constant drug release over time, which is associated to the mechanism of the process. The drug release mechanism of HPMC contained tablets is based on their high degree of water absorption, hydration and swelling, forming of outer pseudo-gel layer, which control the drug release from the inside toward the surface of the tablet. Chain disentanglement begin when the outer polymer layer is fully hydrated, i.e. erosion of the matrix. The rate of erosion is related to the molecular weight over a wide range by an inverse power low. In addition, erosion rate is affected by the qualitative composition and by the amount of drugs and other additives within the matrix. The increase of the matrix carrier Kollidon® SR concentration (31.25% for model M9 and 37.5% for model M10), leaded to significant decrease of the drug release properties of the system, as model M10 released about 60% of the drug for 6 hours.

The dissolution profiles of models M1-M4, depended on two factors: (i) quantity of Methocel® K100LV, which was represented at two levels (75.0 mg and 150.0 mg in a dosage unit) and (ii) quantity of Kollidon® VA64, which was also represented at two levels (15.0 mg and 45.0 mg in a dosage unit). In order to evaluate the degree of interactive influence of the two factors on the drug release rate from the dosage form, the time required for 50% of the drug release (T_{50}) was calculated (Table 3) and the results were used for construction of three dimensional (3D) response surface plot (Figure 4).

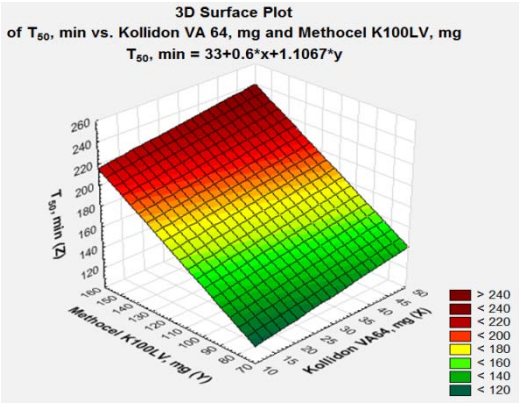

Figure 4: Threedimensional (3D) response surface plot, which represents the interactive influence of two factors on the T_{50}.

Figure 4 shows the 3D plot of the effect of factors X (quantity of Methocel® K100LV) and Y (quantity of Kollidon® VA64) on the response Z (time required for 50% of the drug release). At the lowest level of X and Y, Z is 119 min, while at the highest level of X and Y, Z is 220 min (Table 3).

The equation, which represents the dependence of the response Z from the factors X and Y is:

$$Z = 33 + 0.6 \times X + 1.1067 \times Y.$$

It can be noticed that an increase of the Kollidon® VA64 amount in one dosage unit, had higher influence on the retention properties of the system when Methocel® K100LV was used in lower concentration (25%). Also, from the slope of the X and Y axis, it can be uncovered that Methocel® K100LV had a more substantial effect on the retention properties of the formulation.

The data from *in vitro* drug release were fitted to different kinetic models (Table 3).

For models based on HPMC the highest correlation coefficients were obtained by fitting drug release data with Square root model (for models M1-M4, R = 0.995 to 0.999 and for models M5-M7, R = 0.988 to 0.999). Drug release profiles for models M8-M10 (based on Kollidon® SR) showed good linearity with first order kinetic (R = 0.981 to 0.997) and Square root model (R = 0.983 to 0.996). All results, which were gained (Table 3) indicated a diffusion drug release mechanism. To confirm this finding, the data were fitted to Korsmayer-Peppas model and all formulations showed good linearity (R = 0.967 to 0.999). In all 3 types of compositions (M1-M4, M5-M7 and M8-M10) the diffusional exponent (n) values increased with an increase of the polymer quantity. This denotes that in lower polymer concentration (25%) diffusion (quasi-Fickian diffusion (case I transport)) was the dominant mechanism of drug release, while in higher polymer concentration (37.5% and 50%) non-Fickian or anomalous release was the dominant mechanism. In the second case the release was dependent on both drug diffusion and polymer erosion.

CONCLUSION

Model matrix systems based on Methocel® K100LV, Methocel® K4M, Kollidon® VA64 and Kollidon® SR with different polymer concentrations containing galantamine hydrobromide were developed. Influence of both factors swelling and erosion rate on the parameters of the systems was investigated, and the results showed varying degrees of swelling and erosion rate depending on the polymer carrier type and its quantity. *In vitro* drug release studies showed that the increase of polymer content leads to enhancement in the retarding properties of the formulations.

Data from *in vitro* drug release studies were fitted to different kinetic models and the best results for correlation coefficient were obtained for first order kinetic model and Higuchi model, which indicates a diffusion drug release mechanism. The most perspective model for sustained galantamine hydrobromide release is M6 based on Methocel® K4M with over 80% released drug for 8 hours.

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