Research Article

Development of Eudragit Based Sustained Release Systems of Galantamine Hydrobromide

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ABSTRACT

Alzheimer's diseaseis one of the most severe diseases affecting people today. Nowadays, galantamine hydro bromide is used as an effective treatment for mild to moderate dementia of the Alzheimer's type. The aim of this study is to develop drug delivery systems with prolonged release of galantamine hydro bromide. Retarding agents in this process are the hydrophobic polymers Eudragit® RL and Eudragit® RS. Design of experiments is used to investigate the main factors influencing the release characteristics of the drug substance. Several studies for compatibility between galantamine hydro bromide and the excipients, swelling rate and erosion rate are performed. Furthermore, an in vitro drug release study is carried out and various mathematical models are used in order to evaluate the kinetics and the drug release mechanism. The data show that the galantamine hydro bromide release mechanism from all tested systems is diffusion-controlled.

Keywords: Alzheimer's disease, Drug delivery systems, Galantamine hydro bromide, Matrix tablets, Sustained drug release.

INTRODUCTION

One of the main directions of the modern pharmaceutical technology is sustained-release drug delivery systems. Their advantages include less fluctuation of the drug levels in the blood, reduced dosage frequency, reduction of adverse side effects, improved patient compliance and reduction of overall healthcarecosts.[1] Moreover, as industrial products, they permit high levels of reproducibility, stability of raw materials, easy scale-up and validation of the manufacturing process.[2] Their development is mainly based on improving the properties of the polymeric carrier and the efficiency of drug release systems. Synthetic poly(meth)acrylates, known as Eudragit®, are commonly used in the pharmaceutical development of sustained-release dosage forms.[3,4] This is due to their chemical stability and biocompatibility, as well as their good technological parameters.[5-7]

Galantamine hydro bromide belongs to the group of cholinesterase inhibitors. It is a reversible, competitive inhibitor of the enzyme acetylcholinesterase.[8] Its main indication is the treatment of mild to moderate dementia in people with Alzheimer's disease, at a dose of 16-24 mg per day.[9-11] Galantamine hydro bromide 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 to reach the maximum plasma concentration (t_{max}) is approximately 1 hour.[12] According to the Biopharmaceutics Classification System (BCS), galantamine belongs to class I - drugs with high solubility and high permeability.[13]

The aim of this study is to develop matrix systems, which contain galantamine hydro bromide based on different combinations of Eudragit® RL and Eudragit® RS as sustained drug delivery polymers. For this purpose, the influence of the quantity and the type of the polymeric carrier on the technological and biopharmaceutical parameters of different model compositions has been investigated. The mechanism of drug release from the obtained systems has also been studied.

MATERIALS AND METHODS

Materials

Galantamine hydro bromide (Sopharma PLC, Bulgaria), ammonio methacrylate copolymer, type A (Eudragit® RL PO - Evonik, Germany), ammonio methacrylate copolymer, type B (Eudragit® RS PO - Evonik, Germany), lactose monohydrate (Tablettose® 70 – Meggle, Germany), magnesium stearate (Magnesia, Germany); colloidal silica dioxide, anhydrous (Aerosil® 200 – Evonik, Germany).

Methods

Compatibility studies

Possible chemical interactions between galantamine hydro bromide and the excipients are investigated by isothermal stress testing (IST). Binary mixtures, each containing galantamine hydro bromide and one excipient are placed in hermetically sealed glass vials and are stored at the temperature of 60° C for a period of 4 weeks. The water absorption in the system, acting as medium or a plasticizer for the reactive substances could increase the reactivity. In order to study the influence of water content in the system, each binary mixture is prepared twice. For every second version 20% of water is added based on the dry substances.[14] A sample containing only galantamine hydro bromide is used as reference. At a predefined period, the samples are

analyzed for related substances (impurity E (N-desmethyl galantamine), nonspecific impurity and total impurities). The amount of the impurities is determined by liquid chromatography using HPLC equipment (Dionex ICS-5000+, USA). Before operating, the mobile phase is filtered through a membrane filter with a pore size of 0.45 µm and degassed. Parameters of determination are as follows: Flow rate - 1.0 ml/min, wavelength - 287 nm, time for chromatography -40 min, the volume of injection - 10 µl, column temperature -30°C.

Preparation of model matrix systems

Model matrix systems, which contain galantamine hydro bromide, polymer carriers and excipients are prepared by direct compression using a rotary tablet press (Fette 52i, Germany), provided with punch and die tooling designed for round biconvex tablets 9 mm in diameter. All samples are prepared under the same parameters of the tablet press - pre-compression force 2-3 kN, main-compression force 10-12 KN, "dwell time" 50-55 msec. The weight of each tablet is 300 mg.

Factorial design

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

$y_{ijk} = \mu + \alpha_i + \beta_j + \alpha\beta_{ij} + \varepsilon_{ijk}$ ..... (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 $\varepsilon_{ijk}$is a random effect due to sampling.[15]

Investigation on swelling and erosion kinetics of the matrix tablets

The test is performed using the method described by Reynold et al.[16] The tablets are accurately weighed and immersed in 50 ml PBS (pH 6.8), at 37˚C. The tablets are taken out in predefined intervals (up to 8 hours). Water from the surface is carefully removed by blotting with filter paper and the weight is measured. After that tablets are dried to a constant weight for a period of 48 h,at 50˚C in a vacuum drier. The swelling of matrix tablets and their erosion, average of 6 tablets, are calculated using the next equations:

$Swelling(\%) = (W_s - W_d)/\ W_d \times 100$..... (2)

Where W_s and W_d are the weights of the swollen and the dry tablets respectively.

$Erosion(\%) = (W_t - W_d)/\ W_t \times 100$..... (3)

Where W_t is the initial mass of the tablet.

***In-vitro* drug release studies**

The test is performed using apparatus 2 – paddle dissolution test, according to USP - SOTAX AT 7 (Switzerland). The test is 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 are immersed in 0.1 M HCl solution (pH 1.2) for 2 hours and then the pH of dissolution media is changed to 6.8 (PBS). Samples of 5 ml are withdrawn at selected intervals up to 8 and replaced with 5 ml of fresh media. Each sample is filtered through a 0.45 µm membrane filter (Sartorius cellulose acetate filter, Germany). The amount of the drug released is determined from UV absorbance at 288 ± 2 nm using Hewlett-Packard 8452 A Diode Array spectrophotometer (New Jersey, USA). The cumulative percentage of drug release is calculated and the average of six determinations is used in data analysis.

Study of drug release kinetic

The kinetics of drug release from matrix tablets are determined by fitting different curves to distinct models. The models included are:

Zero order kinetic

$M_t = k_0 t$..... (4)

First order kinetic

$M_t = M_0 . e^{-k_1 t}$..... (5)

Higuchi's square root model[17]

$M_t = k_2\sqrt{t}$..... (6)

Korsmeyer-Peppas model[18]

$M_t / M_\infty = kt^n$..... (7)

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_0, k_1, k_2 are the release constants; kis a constant incorporating the structural and geometric characteristics of the drug dosage form and n is the release exponent.

The following methods are used for comparison of dissolution profiles of different matrix tablets:[19, 20]

Similarity factor (f_2)

Similarity factor is calculated by the equation:

$f_2 = 50\log\{[1 + \left(\frac{1}{n}\right)\sum_{i=0}^{n}(R_i - T_i)^2]^{-0.5} \times 100\}$,..... (8)

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.

Mean dissolution time (MDT)

MDT is expressed by the formula:

$MDT = \frac{\sum_{j=1}^{n} \hat{t}_j \Delta M_j}{\sum_{j=1}^{n} \Delta M_j}$..... (9)

where:*j* is the sample number, *n* the number of time points for sample taking, $\hat{t}_j$ is the average point between t_j and t_{j-1}, and ΔM is the additional quantity of drug dissolved between t_j and t_{j-1}.

RESULTS AND DISCUSSION

Compatibility studies

Possible chemical interactions between galantamine hydro bromide and the excipients (binary mixtures) in the

compositions are investigated by isothermal stress testing (IST). The influence of the water content on stability of the systems is also investigated and the obtained results are represented in table 1.

Table 1: Isothermal stress data

Substances	Drug/ excipient ratio	Water %	Unspecified substances, %		
			Impurity E	Unidentified impurity	Total impurities
Galantamine HBr	-	-	0.41	0.06	0.47
Galantamine HBr	-	20	0.43	0.06	0.48
Galantamine HBr + Tablettose® 70	1:5	-	0.43	0.06	0.49
Galantamine HBr + Tablettose® 70	1:5	20	0.42	0.08 ; 0.06	0.56
Galantamine HBr + Magnesium stearate	5:1	-	0.41	0.06	0.47
Galantamine HBr + Magnesium stearate	5:1	20	0.41	0.06 ; 0.14	0.61
Galantamine HBr + Aerosil® 200	10:1	-	0.42	0.06	0.48
Galantamine HBr + Aerosil® 200	10:1	20	0.41	0.07	0.48
Galantamine HBr + Eudragit® RS	1:4	-	0.41	0.12 ; 0.06	0.59
Galantamine HBr + Eudragit® RS	1:4	20	0.42	0.05	0.47
Galantamine HBr + Eudragit® RL	1:1	-	0.43	0.06	0.49
Galantamine HBr + Eudragit® RL	1:1	20	0.53	0.07	0.60

The results from the chemical compatibility show no considerable interaction between galantamine hydro bromide and the excipients. The values of the tested related substances show no substantial difference in comparison with those of a reference sample. In some of the binary mixtures in presence of water negligible increment is observed but the total amount of impurities is not more 1.5%, a limit determined for long-term stability of a final product according to ICH Q1A(R2).[21]

Preparation of model matrix systems

A full factorial design - 3^2 (two factors on three levels) is used to investigate the influence of two variable factors on the release characteristics of galantamine hydro bromide. In this regard, nine trials (M1-M9) are included. The first factor is the quantitative ratio of the two polymer carriers (Eudragit®RS and Eudragit® RL) at three levels: 80:20; 90:10 and 95:5 and the second factor is the percentage of the polymers at three levels: 25%, 37.5%, and 50% from the weight of tablet composition (table 2).

Based on experimental domain, nine experimental models of matrix tablets (M1-M9) are prepared. All models contain 37.77 mg galantamine hydro bromide (equivalent to 24 mg galantamine) and different quantities of both matrix polymers, Eudragit® RS and Eudragit® RL, according to data presented in table 2. The tablets contain also Tablettose® 70 as a filler, magnesium stearate as a lubricant and Aerosil® 200 as a glidant. The total weight of the tablets is 300.0 mg. The technological properties of the models shown in table 3 indicate that all model formulations meet the requirements of the Eur. Ph. 7.0.

Table 2: Experimental domain of the study

Model	Eudragit®RS/ Eudragit® RL ratio, %	Quantity of the polymers in the tablet composition, %
M1	95:5	25.0
M2	95:5	50.0
M3	90:10	37.5
M4	80:20	50.0
M5	80:20	37.5
M6	80:20	25.0
M7	95:5	37.5
M8	90:10	50.0
M9	90:10	25.0

Investigation on swelling and erosion rate of the matrix systems

Three formulations are investigated for swelling and erosion rate of the matrices (table 4, figure 1): Model M2with highest polymer content (50%) and the highest quantity of Eudragit®RS (95%); model M4 with the highest polymer content (50%) and the lowest quantity of Eudragit®RS (80%) and model M6 with the lowest polymer content (25%).

All models consistently showed an increase of swelling and erosion with time. A rapid penetration of water into the tablet for the first 30 min is observed, followed by slower and constant water uptakes.The results for both models M2 and M4 demonstrate similar swelling and erosion properties. Model M6 displays faster swelling and erosion rate and maximum water absorption is reached up to the 5^{th} hour, while for models M2 and M4 maximum water absorption is achieved up to the 8^{th} hour. It is a logical result taking into consideration that models

M2 and M4 contain a larger quantity of matrix polymers in comparison with model M6. High values of the swelling correlation coefficient (R) after 30 min are obtained (figure 1), and the data for models M2, M4 and M6 are 0.920, 0.926 and 0.988 respectively. Similar results are observed and the data for models M2, M4 and M6 are 0.949, 0.958 and 0.972 respectively.

Table 3: Technological parameters of the matrix tablets

Model	Resistance to crushing		Uniformity of mass		Uniformity of dosage units, AV
	Average, N	% RSD	Average, g	% RSD	
M1	81.70	4.48	0.299	1.16	3.3
M2	79.60	5.78	0.300	0.97	4.2
M3	81.10	5.07	0.299	0.85	3.7
M4	80.30	4.72	0.300	1.04	5.2
M5	82.30	5.37	0.302	0.94	4.3
M6	83.90	4.65	0.300	0.92	3.8
M7	81.80	5.59	0.301	1.02	2.9
M8	80.10	4.16	0.301	1.12	4.1
M9	81.50	4.82	0.300	0.89	3.5

Table 4: Matrix swelling and erosion rate data

Time, h	Model M2		Model M4		Model M6	
	Swelling, %	Erosion, %	Swelling, %	Erosion, %	Swelling, %	Erosion, %
0.5	26.2	9.7	26.4	11.1	24.3	12.3
1	29.6	14.3	28.6	12.6	28.7	18.7
2	34.8	18.7	34.8	17.4	51.5	32.0
3	43.4	24.7	42.2	21.1	62.0	37.7
4	47.7	27.3	49.8	24.7	78.7	43.7
5	48.1	28.7	53.1	27.3	100.0	50.7
6	54.9	32.0	56.5	29.8	-	-
7	58.9	34.3	60.3	32.3	-	-
8	63.7	36.7	63.9	34.7	-	-

Table 5: Drug release kinetics

Model	Zero order (R)	First order(R)	Higuchi Model (R)	Korsmeyer-Peppas model		MDT (h)
				R	*n*	
M1	0.877	0.999	0.981	0.981	0.41	1.18
M2	0.925	0.947	0.995	0.996	0.45	1.72
M3	0.906	0.990	0.992	0.993	0.43	0.94
M4	0.927	0.981	0.998	0.999	0.43	1.29
M5	0.889	0.986	0.987	0.993	0.39	0.83
M6	0.838	0.998	0.965	0.965	0.35	1.07
M7	0.915	0.989	0.995	0.995	0.45	0.99
M8	0.911	0.998	0.991	0.997	0.41	1.59
M9	0.869	0.990	0.975	0.971	0.40	1.14

In-vitro drug release studies

In order to determine the conditions of in vitro test, the test of model M2 is performed at two different pH medium: (i) pH 6.8 and (ii) in changing pH (2 hours in pH 1.2 and for the rest of time in pH 6.8). The results presented in figure 2show that the release of galantamine hydro bromide from the model is pH independent, which is confirmed by calculations of similarity factor f_2 = 69.32. Based on these results, further tests are performed in dissolution medium with pH 6.8.

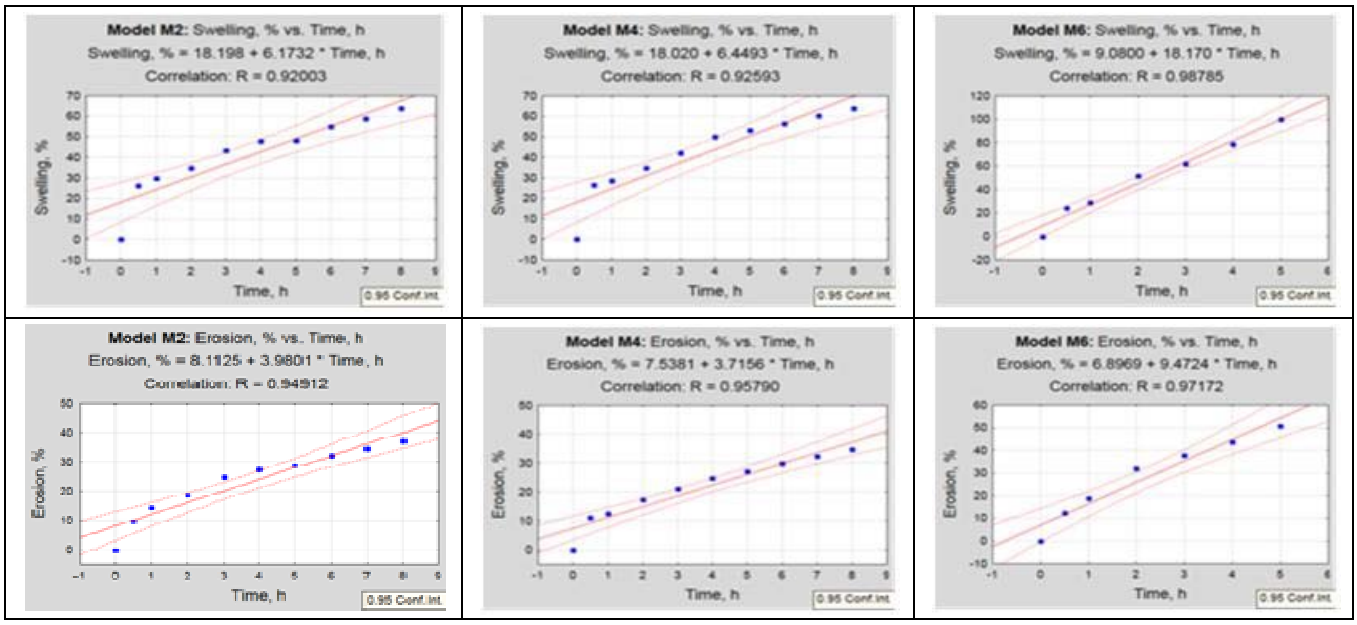

Figure 1: Correlation between swelling rate vs. time and erosion rate vs. time for models M2, M4 and M6

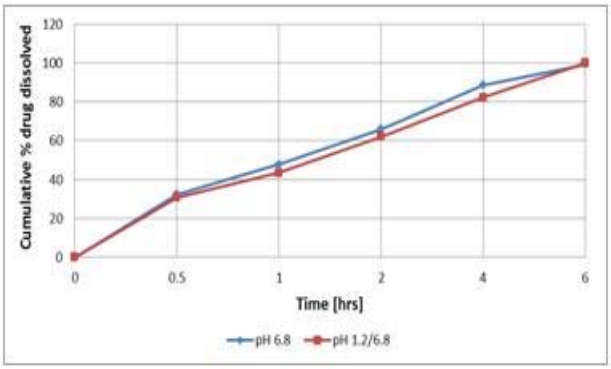

Figure 2: A comparative dissolution profile of the model M2 in a dissolution medium pH 6.8 and in changed pH medium.

The galantamine hydro bromide release profiles of models M1-M9 in dissolution medium with pH 6.8 are presented in figure 3.

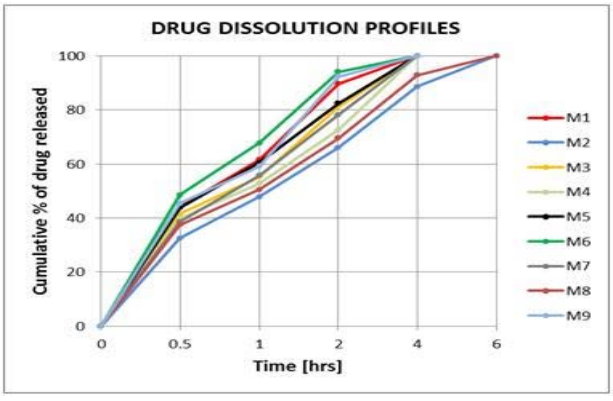

Figure 3: Release kinetics of galantamine hydro bromide from the model matrix tablets (M1-M9) in dissolution medium with pH 6.8

The release profiles presented in figure 3 show differences in release rate of the drug from different models. The fastest drug release is observed for models M1 and M6 containing the lowest percentage of polymers (25%),and the slowest drug release from models M2 and M8 with the highest content of polymer (50%) in the matrix. The first two models release about 20% more galantimin hydrobromide to the first hour compared to the models M2 and M8. Furthermore, models M1 and M6 release about 100% drug up to 4 hours while models M2 and M8 sustained galantamine release up to 6 hours. It should be noted that both models M2 and M4 with equal polymer content (50%) but with different quantitate ratio show different drug release rate. Model M2 with 95:5 of Eudragit® RS/Eudragit® RL ratio shows 20% delay of drug release in comparison to model M4 with 80:20 polymers ratio. Therefore, it could be concluded that both factors - the total content of the polymers in the formulation and their quantitative ratio influence the drug release rate of the from matrix systems.

In order to evaluate the degree of interactive influence of the two factors on the drug release rate from the dosage form,the mean dissolution time (MDT)is calculated (table 5) and the results are used for construction of threedimensional (3-D) response surface plot (figure 4).

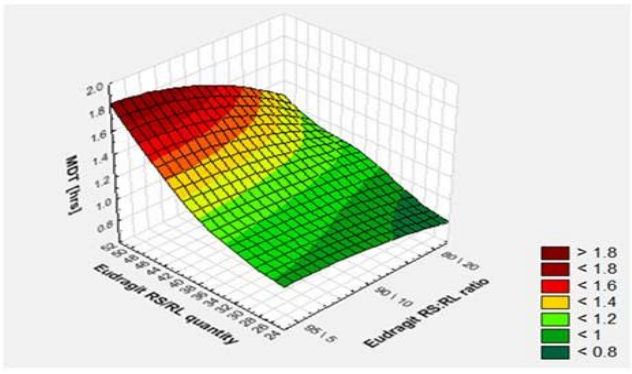

Figure 4: Threedimensional (3-D) response surface plot, which represent the interactive influence of two factors on the MDT.

The plot displayed on figure 4 shows the influence of the both evaluated factors: total polymer quantity and the polymer ratio on the mean dissolution time of the drug. It can be noticed that increasing of the total amount of polymers in one dosage unit, and the quantity of slightly water permeable Eudragit® RS results in an increment of the retention properties of the matrix system.

The data from in vitro drug release are fitted to different kinetic models (table 5).

The highest correlation coefficient obtained by fitting drug release data with first order kinetic (R = 0.947 to 0.999) and Higuchi model (R = 0.965 to 0.998) indicates a diffusion drug release mechanism. To confirm this finding, the data are fitted to Korsmayer-Peppas model and all formulations show good linearity (R = 0.965 to 0.999). The diffusional exponent (n) values ranging from 0.35 to 0.45 denote that diffusion (quasi-Fickian diffusion (case I transport)) is the dominant mechanism of drug release.

CONCLUSION

Modelmatrix systems based on Eudragit® RS and Eudragit® RL with different polymercompositions containing galanthamine hydrobromideare developed.A compatibility study between the drug substance and the excepientsshow a lack of significant interactions and results within the predetermined limits. It is estimated by factorial design that the optimal number of experiments and variations of the polymercompositions are nine. Influence of both factors swelling/erosion rate on the parameters of the systems is found. In vitro drug release studies show that both the increase of polymer content and the presence of a larger amount of Eudragit® RS in matrices lead to enhancement in the retarding properties of the formulations. Data from in vitro drug release studies are fitted to different kinetic models and the best results for correlation coefficient are obtained for first order kinetic model and Higuchi model, which indicates a diffusion drug release mechanism. The most perspective model for sustained galantamine hydro bromide release is the model M2 with 50% total polymer content and 95:05% Eudragit® RS and Eudragit® RLratio.

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