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# Technological and Biopharmaceutical Properties of Galantamine Hydrobromide Based Matrix Systems

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**Abstract:** Sustained drug release systems, containing cholinesterase inhibitor galantamine hidrobromide have been developed, aiming to complement the treatment options for Alzheimer's disease, by controlling the release profile of drug substance. Matrix tablet compositions were prepared by the method of direct tableting, based on the hydrophilic hydroxypropyl methylcellulose (Methocel® K4M) and the hydrophobic polyvinyl acetate/povidone (Kollidon® SR). All compositions were assessed by dynamic tests in order to determine the relation between compression force, solid fraction and tensile strength of the tablets. Uniformity of mass and the active substance content uniformity were studied by using the statistical method of Six Sigma. *In vitro* investigation on the active substance dissolution profile was conducted and it revealed influence of the type and the quantity of the polymer onto the technological and biopharmaceutical properties of all developed systems.
**Keywords:** galantamine hydrobromide, drug delivery systems,sustained drug release, matrix tablets.

## Introduction

Acetylcholinesterase inhibitors represent first-line therapy for patients with mild to moderate Alzheimer disease and they improve their cognitive, physical and social functions. In such cases,galantaminehydrobromide equivalent to a daily dose of 16-24 mg galantaminebase, is used for medical treatment.[1,2]Galanthamine 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.[3]According to the Biopharmaceutics Classification System (BCS), galantamine hydrobromide belongs to class I - drugs with high solubility and high permeability.[4]

Due to the specific therapeutic use, the possibility of includinggalantamine hydrobromide into a sustained release systems would be very appropriate becauseoftheir ability to reduce the side effects and lower the frequency of administration. This leads to increased comfort and improved patient compliance, especially important for those, who are submitted to a chronic medication regiment.[5] One of the most commonly used methods for controlled release formulations development is direct compression as they can be easily manufactured with conventional tableting facilities and their preparation involves few processing variables.[6]During the past few years, a new approach named Quality by design (QbD) has been used by many pharmaceutical researchers, in order to detect the relationship between the product quality and the process parameters. As tableting is one of the most crucial stages in the direct compression method of manufacturing, it is important to study it into details while examininsome technological characteristic of the tablet mixture.The last will provide valuable data about issues,such as whether the compression occurs mainly by plastic deformation or by particle fragmentation; is there a significant material adhesion on the die wall, which can

affect negatively the processand what is the reproducibility of the tableting process in a long term production. Information about the material compression characteristics can be obtained by using the Heckel plot or Kawakita equation, which demonstratethe influence of the applied compression force on the resulting compact, and hence the optimal parameters to produce a strong enough tablet structure.[7]Furthermore the study of the ejection force and its relation with the applied pressure is valuable when trying to optimize the tableting process, in order to obtain tablets with desirable mechanical strength.

Two critical quality attributes,whichare tightly limited by the European Pharmacopoeia (Ph. Eur.) are in great significancefor the investigation of the tableting process reproducibility - uniformity of mass and uniformity of content.In this regard, the use of the Six Sigma method makes it possible to assess the capability of the tableting process under production conditions.[8]

Another very crucial and important aspect of the development of sustained release formulations is the correct selection of polymer carrier. This study was focused on Hydroxypropyl methylcellulose (HPMC) as a hydrophilic matrix agent, suitable for direct compression because of its good flowability and compressibility.[9]Kollidon® SR was selected as a hydrophobic polymer carrier containing polyvinyl acetate and polyvinylpyrrolidone in a physical mixture. Kollidon® SR represents excellent flowability and the tablets based on this polymer are characterized by low friability and high mechanical strength due to the combination of the very plastic polyvinyl acetate and the strongly binding povidone.[10,11] A different behavior is observed with these two polymers in contact with aqueous fluids. HPMC forms a viscous gel layer through which the drug is released by diffusion and/or by erosion.[12] Unlikethe latter, the polyvinylpyrrolidone component of Kollidon® SR gradually dissolves creating pores for the drug to diffuse out, while the polyvinyl acetate component maintains tablet core structure during dissolution.[13]

The aim of this research is development of Methocel® K4M and Kollidon® SR based matrix systems containing galanthamine hydrobromide and determination of the influence of the type and the quantity of the polymers on the technological and biopharmaceutical parameters of the obtained systems.

## Materials and Methods

### Materials

Galantamine hydrobromide (Sopharma PLC, Bulgaria), Hypromellose, nominal viscosity 4000 mPa·s (Methocel® K4M Premium CR - Dow Chemical Co., USA), Polyvinyl acetate and povidone based matrix forming agent (Kollidon® SR, BASF SE, Germany), Lactose monohydrate (Tablettose® 70 – Meggle, Germany), Magnesium stearate (Magnesia, Germany) and Silica, colloidal anhydrous (Aerosil® 200 – Evonik, Germany)are used in preparation of tablets.

### Methods

#### Obtaining of model matrix systems

All model matrix systems contained 30.77 mg galantamine hydrobromide (equivalent to 24.0 mg galantamine base), different quantities of matrix polymers and other functional excipients. The systems were prepared by the method of direct compression. Tabletting was carried out on a rotary tablet press (Fette 52i), provided with compression tools, designed to produce round biconvex tablets with a diameter of 9 mm. In order to investigate the influence of compression pressure on technological properties of the tablets, various forces were used in the range of 5-16 KN at “dwell time” 50-55 ms.

#### Technological properties of the tablets

#### Mechanical strength

The mechanical strength of the tablets was measured by radial breaking, by using apparatus Erweka type TBH 30, Germany.

**Heckel plot**

The Heckel equation express the change of the powder density with the applied compression pressure:[14]

$$\ln[1/(1-D)] = kP + A$$

where, *P* is the applied compression pressure, *D* – the relative density of the tablet at pressure *P*, hence *1 – D* is the porosity of the tablet at pressure *P*. The constant *A* is suggested to reflect particle rearrangement and fragmentation. The constant *k* is derived from the slope of the linear part of*ln[1/(1 - $\rho_r$)]* against *P* plot. The reciprocal of the slope value *k* is considered to represent a material dependent constant known as the yield pressure $P_y$, which is defined as the compression pressure at which plastic deformation of material is initiated.

**Kawakita equation**

The Kawakita equation studies the dependence of powder densification (as volume reduction) withthe applied compression pressure:[15]

$$P/C = P/a + 1/ab$$

where, *P* is the applied pressure, *C* is the relative volume decrease, i.e. $C = (V_0 - V_p)/V_0$ ($V_0$ is the initial powder bed volume and $V_p$ is the powder volume upon compression). The constants *a* and *b* can be derived from a *P/C* against *P* plot. It is shown that the constant *a* is equal to the initial porosity. The constant *b*, has the dimension of the reciprocal of the pressureand is related to the plasticity of the material. The reciprocal of *b* is known as $P_k$, which is the pressure required to reduce the powder bed by 50%. The lower the value of $P_k$, the higher degree of plastic deformation isoccurring during compression.[16]

**Ejection force**

The ejection force is the force, which is required to overcome the friction between the die wall and the tablet.[17] It is expressed as:

$$F_d = \mu . F_r$$

where, $F_d$ is the lost force due to the friction between the die wall and the tablet, $F_r$ is the radial force, and $\mu$ is friction coefficient.

When preparing tablets with different applied compression pressure, ejection forces (EF) with different values is generated.

**Compactability, Tabletability, Compressability**[18]

*Compactability* is the relationship between tensile strength (σ) and solid fraction (SF) content of the tablet. The tensile strengthis expressed by the following equation:

$$\sigma = 2F/\pi dh$$

where, *F* is the hardness of the tablet (N), *d* and *h* are the diameter and the thickness of the tablet, respectively.

Solid fraction content is estimated by the equation:

$$SF = W_t/\rho_{true}V$$

where, $W_t$ is the tablet weight, $\rho_{true}$ is the powder true density, *V* is the tablet volume.

*Tabletability* is the relationship between tensile strength (σ) and applied compression pressure (P).

*Compressability* is the relationship between applied compression pressure and solid fraction content.

The influence of the particular factors on compactability, tabletability and compressability was studied graphically by Response Surface Methodology (RMS), creating three dimensional surface plot (3-D plot). [19]

**Uniformity of mass and uniformity of content**

The two quality items were studied fortableting process reproducibility. For that purpose the statistical method Six Sigma wasused, based on ± 6 times the standard deviation. [20] It is expressed by the following equation:

$$C_{pk} = \min[(USL - X_{mean})/3\sigma, (X_{mean} - LSL)/3\sigma]$$

where $C_{pk}$ is process capability index, *USL* is upper specification limit, *LSL* is lower specification limit, $X_{mean}$ is mean value and $\sigma$ is the standard deviation of the trial.

***In vitro* drug release studies**

The test was performed 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 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.

## Results and Discussion

**Obtaining of model matrix systems**

All matrix systems compositions are presented intable 1.

**Table 1. Matrix systems compositions**

| Ingredient | Model | | | | | |
|---|---|---|---|---|---|---|
| | M1 [mg] | M2 [mg] | M3 [mg] | M4 [mg] | M5 [mg] | M6 [mg] |
| Galantamine hydrobromide | 30.77 | 30.77 | 30.77 | 30.77 | 30.77 | 30.77 |
| Tablettose® 70 | 188.23 | 150.73 | 113.23 | 188.23 | 150.73 | 113.23 |
| Methocel® K4M | 75.0 | 112.5 | 150.0 | - | - | - |
| Kollidon® SR | - | - | - | 75.0 | 112.5 | 150.0 |
| Aerosil® 200 | 3.0 | 3.0 | 3.0 | 3.0 | 3.0 | 3.0 |
| Magnesium stearate | 3.0 | 3.0 | 3.0 | 3.0 | 3.0 | 3.0 |

**Investigation of the technological properties of the models**

In order to investigate the technological properties, two models containing 25% of a hydrophilic and of a hydrophobic matrix polymer (M1 and M4) were chosen.

### Heckel plot

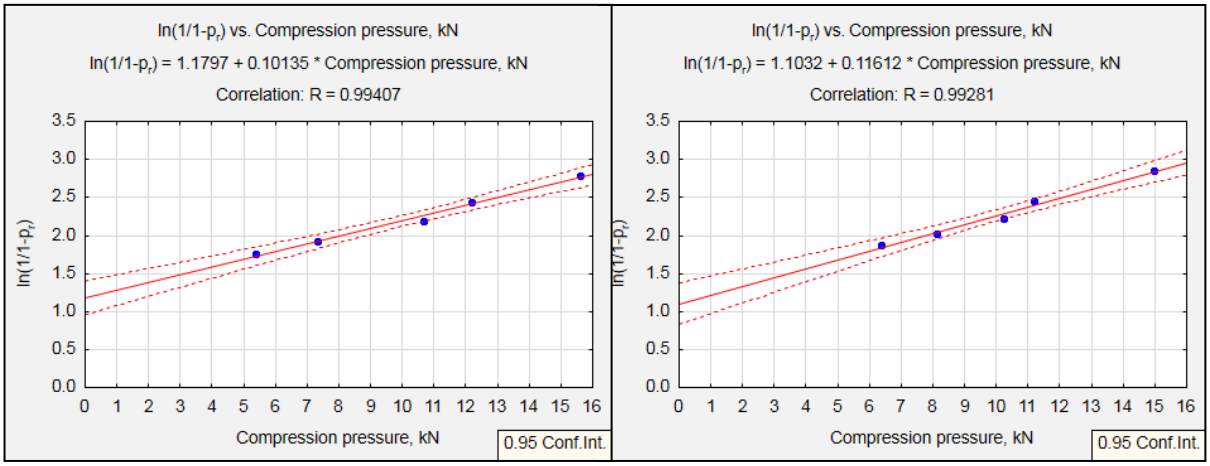


**Figure 1. Regression analysis of models M1 (left) and M4 (right), which displays the dependence of the tablets density variation from the applied compression force**

The dependence of the tablets density variation from the applied compression force is presented in figure 1.

The parameters obtained from the two Heckel plots are presented in table 2.

**Table 2*:* Results from the Heckel analysis**

| Model | k | $P_y$ (kN) | R | p-value |
|---|---|---|---|---|
| Model M1 | 0.1013 | 9.87 | 0.994 | 0.000547 |
| Model M4 | 0.1161 | 8.61 | 0.993 | 0.000731 |

A very strong correlation between the two variables was observed, with high correlation coefficients. The two p-values showed high significance levels of the results. It is well known that materials with low yield pressure ($P_y$) undergo plastic deformation, while these with high yield pressure are more brittle and consolidate mainly via fragmentation. [21]The obtained data revealed the plastic deformation occurs at lower pressure with model M4 based on Kollidon® SR in comparison to model M1 ($P_y$ is 8.61 and 9.87 respectively).From the data presented it could be suggested that the compression pressure of about 10 kN was sufficiently to form robust and stable tablet structure in both models.

### Compaction according to Kawakita equation

The data from the investigation of the tablet densification(P/C) as function of the applied compression pressure are presented in figure 2.

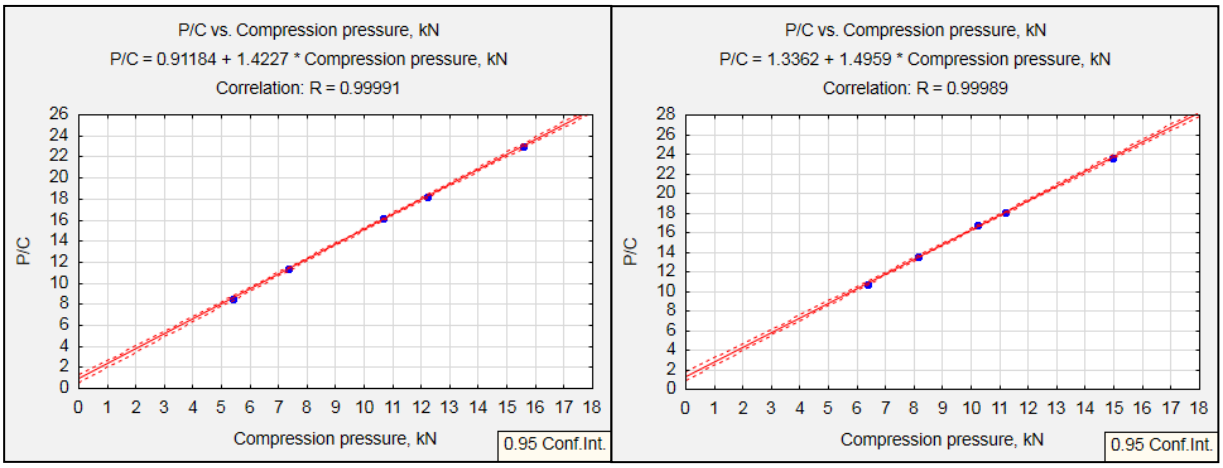


**Figure 2. Dependence of tablet mixturedensificationfrom applied compression pressure, according to the Kawakita equation - model M1 (left) and model M4 (right)**

The parameters obtained from the two graphics based on the Kawakita equation are presented in table 3.

**Table 3:Kawakita analysis results**

| Model | a | b | $P_k$ (kN) | R | p-value |
|---|---|---|---|---|---|
| Model M1 | 0.703 | 1.560 | 0.641 | 0.999 | 0.000001 |
| Model M4 | 0.668 | 1.120 | 0.893 | 0.999 | 0.000001 |

It was observed very strong correlation between the two variables with high correlation coefficients (R > 0.999). The two p-values showed high significance levels of the results. Higher $P_k$ values were found for model M4, meaning that the system, which contains Methocel® K4M demonstrated better ability to undergo plastic deformation in comparison to the system, based on Kollidon® SR.

**Ejection force**

The dependence of the ejection force from the applied compression force is presented in figure 3.

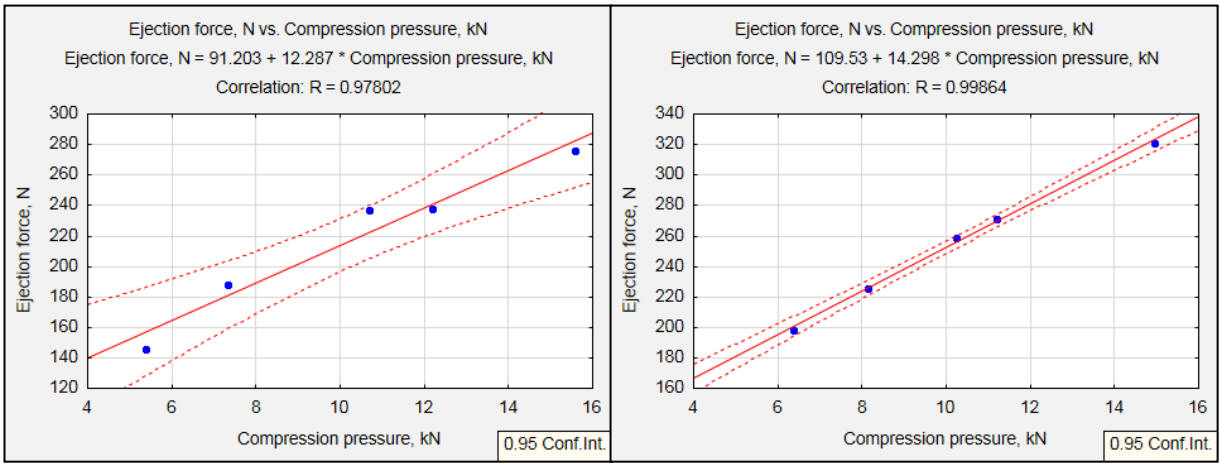


**Figure 3. Dependence of the ejection force from the applied compression force - model M1 (left) and model M4 (right)**

It was observed well expressed linear dependence of the ejection force with the applied compression force in the both tablet models, which was confirmed from the regression coefficients: R = 0.978 for model M1, R = 0.999 for model M4. Higher ejection forces were found for model M4 based on Kollidon® SR, which denotes that this formulation causesmore friction between the tablets and the die wall.

An optimal ejection force is considered to be up to 200 N, although values up to 400 N are accepted as normal. [22]The two graphics indicate that compression forces between 7 and 10 kN producedacceptable results in terms of ejection force.

**Compactability, Tabletability, Compressability**

The results obtained during the study of compactability, tabletability and compressability are presented as 3-D plots in figure 4. Regarding the compactability the dependence between tensile strength (σ) and solid fraction (SF) content was better expressed in model M4, based on Kollidon® SR, in comparison with model M1, based on Methocel® K4M. Mathematically equations excerpted from a bivariate correlation are:

$$\sigma = -904.6 + 1276.5 \times SF$$

with correlation coefficient of R = 0.985 (model M1) and:

$$\sigma = -1269 + 1727.6 \times SF$$

with correlation coefficient of R = 0.954 (model M4).

Regarding the compressability it was observed better dependence between applied compression pressure (P) and the resulted solid fraction content in model M4, in comparison with model M1. Mathematically equations are:

$$SF = 0.70396 + 0.00678 \times P$$

with correlation coefficient of R = 0.985 (model M1) and:

$$SF = 0.71963 + 0.00686 \times P$$

with correlation coefficient of R = 0.947 (model M4).

In the same aspect is tabletability, which reveals better dependence between the applied compression pressure (P) and the resulted tensile strength (σ) at model M4, in comparison with model M1. Mathematically equations about this type of correlation are:

$$\sigma = -9.471 + 9.0028 \times P$$

with correlation coefficient of R = 0.995 (model M1) and:

$$\sigma = -39.02 + 13.110 \times P$$

with correlation coefficient of R=0.999 (model M4).

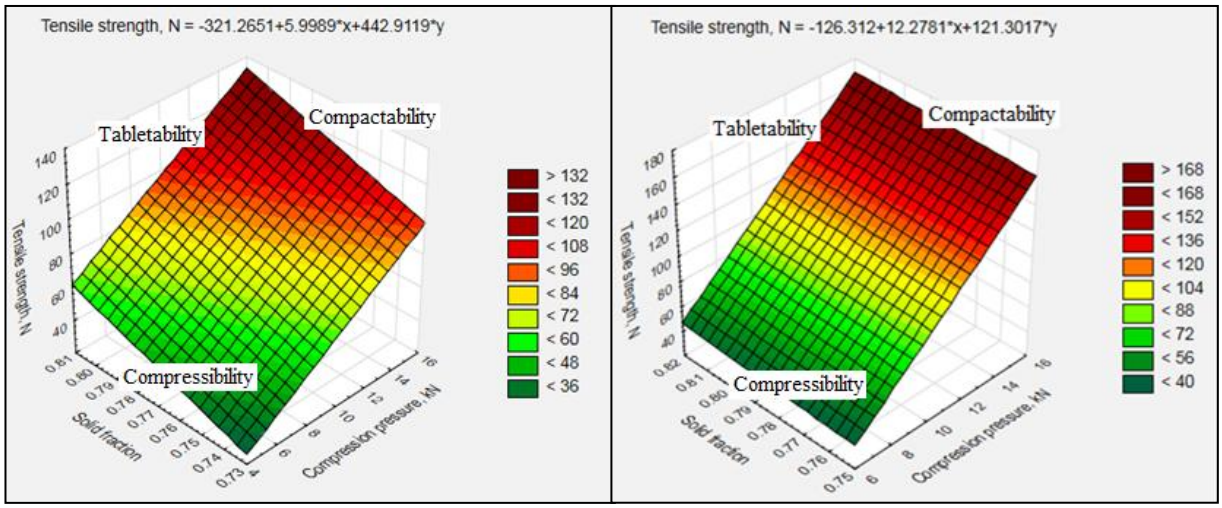


**Figure 4. Three dimentional (3-D)plot of tensile strength, solid fraction and compression pressure for model M1 (left) and model M4 (right)**

**Uniformity of mass and uniformity of content**

The data from the uniformity of mass and the uniformity of galantamine hydrobromide content in the tabletswere evaluated by the statistical tool Six Sigma. The resultsare presented in table 4 and figures 5 and 6.

**Table 4. Process capability regarding uniformity of mass of tablets and uniformity of drug content**

| Model | Uniformity of tablets mass | | Uniformity of drug content | |
|---|---|---|---|---|
| | $C_{pk}$ | Defects per million opportunities (DPMO) | $C_{pk}$ | Defects per million opportunities (DPMO) |
| Model M1 | 1.691 | 0 | 1.670 | 0 |
| Model M4 | 1.757 | 0 | 1.829 | 0 |

Cpk values of 1.33 are required as minimum, while regarding more of the critical items, Cpk values over 1.66 are recommended. [23]

The results presented in table 4 showed highly capable technological process for both models (M1 and M4), regarding the two investigated quality items, which is clear from the high values of $C_{pk}$ (> 1.6). According to the DPMO data, it was well displayed that under the described process circumstances, by 1 million dosage units no one is outside the specification limits of ± 5% for uniformity of tablet mass and ± 15% for uniformity of drug content, limits which are required according to the European Pharmacopeia.

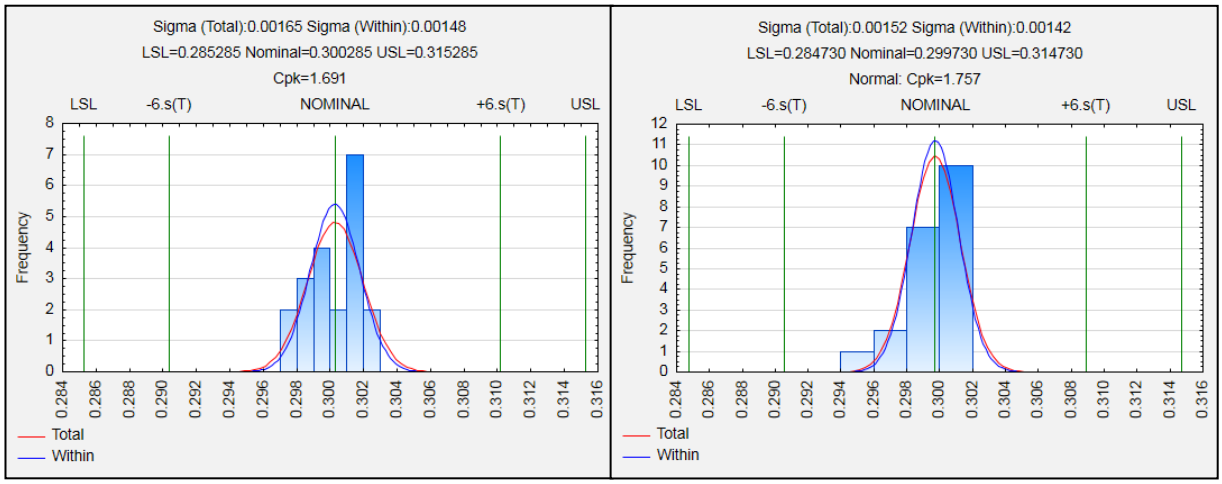


**Figure. 5. Capability of tablets mass uniformity for models M1 (left) and M4 (right)**

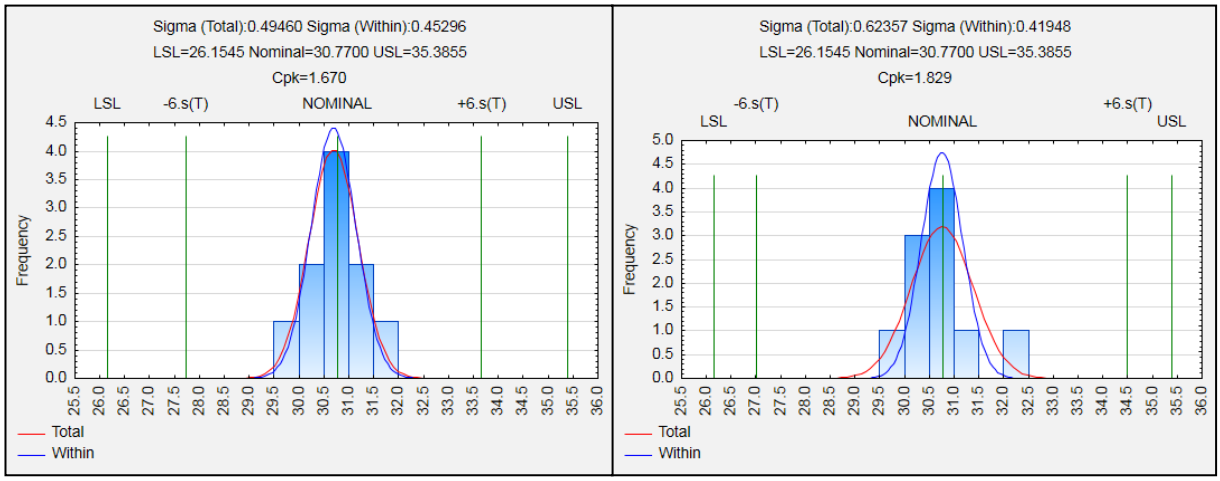


**Figure. 6. Capability of uniformity of drug content for models M1 (left) and M4 (right)**

Regarding the obtained values of $C_{pk}$, better results were displayed from model M4, based on Kollidon® SR, which was due to its excellent rheological properties, consequently better homogenization process of the tableting mixture and more uniformly filling of the die holes.

***In vitro* galanthamine hydrobromide release study.**

In order to determine the conditions of *in vitro* test, the investigation of models M1 and M4 were performed in two different pH medium: (i) in pH 6.8 and (ii) in changed pH medium. The results showed that the release of galantamine hydrobromide from the models is pH independent, which is confirmed by calculations of similarity factor between the two media conditions - $f_2$=81.5 (model M1) and $f_2$=79.7 (model M4).

Dissolution profiles of galantamine hydrobromide for models M1-M6 in medium with pH 6.8 (PBS) are presented in figure 7.

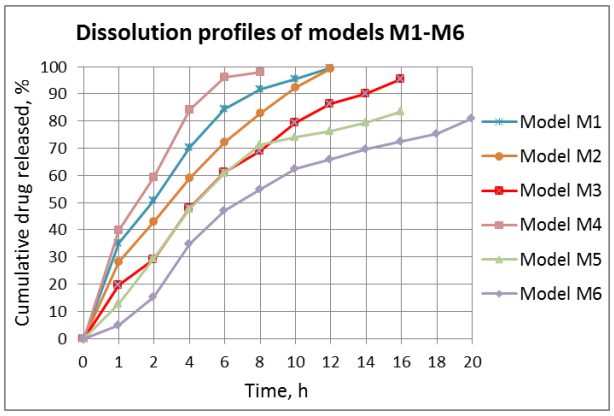


**Figure 7. Dissolution profiles of galantamine hydrobromide from the matrix tablets in medium with pH 6.8 (PBS)**

According to the presented results in figure 7, both the extent and the rate of the drug release depend on the polymer type and the polymer amount in the composition. The two systems with low polymer concentration of 25% (models M1 and M4) demonstrated relatively rapid release of galantamine hydrobromide. From model M4 nearly 100% of the drug was released within 6 hours and from model M1, about 95% of the drug was released for 8 hours.When comparing the two models containing 37.5% polymer (M2 and M5), model M5, which is based on Kollidon® SR indicated enhanced efficacy in the drugdissolution delay.It released less than 80% of the drug for about 16 hours, whilemodel M2released80% of the drug for8 hours.Significant release prolongation was observed from the models containing 50% polymeric carrier (M3 and M6), especially from model M6. It releasedabout80% of the drug substanceafter the 20th hour. It was noteworthy that the increase of the concentration of Methocel® K4M (models M1-M3) led to uniform decrease in the dissolution rate. A different behavior was observed in Kollidon® SR based systems (models M4-M6). While model M4 demonstrated the faster drug release among all compositions,the increase of the polymer concentration reflected in a notable decrease in the dissolution profile.

Based on the conducted *in vitro*drug release studies, it could be considered that the most appropriate model was M2, which is based on 37.5% Methocel® K4M. Itwas released 25% of the drug in the 1st hour, 60% in the 4th hour and more than 80% in the 8th hour.

## Conclusion

Matrix tablets containing 30.77 mg galanthamine hydrobromide (equivalent to 24 mg galanthamine) were prepared. They were based on different types of polymeric carriers, a hydrophilic Methocel® K4M and a hydrophobic Kollidon® SR. Several technological parameters of the prepared model systems were investigated and an expressed process capability of tableting process was observedusing the method of direct tableting. Based on the conducted *in vitro* drug release studies, an optimal composition was obtained by means of the hydrophilic carrier Methocel® K4M in concentration of 37.5% in a dosage unit.

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