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The Application of Mathematical Modeling Tools in Optimizing the Purification Process of the Substance Oligohexamethyleneguanidine Hydrocitrate

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Abstract

The current investigation is dedicated to the use of mathematical modeling, particularly the method of multifactorial analysis of multi-criteria optimization (MAMO) in pharmaceutical development. During the investigation the algorithmic sequence was offered and the necessary tests were provided. The gained data was interpreted through MAMO. The possibility of using the MAMO for solving the applied problem of purifying the oligohexamethyleneguanidine hydrocitrate (OHMG-HC) that is considered to be as a pharmaceutical substance for formation of medicines. The dependencies of purifying conditions that have influence on the final impurities contents and the reasonability of using the suggested algorithm as a means of pharmaceutical development.

Keywords

pharmaceutical development, mathematical modeling, antibiotic resistance, olygohexametyleneguanidines

1 Introduction

The quantity of deaths that were caused by medicine-resistant microorganisms is more than 50000 per year and nowadays the resistance to antimicrobial drugs is considered to be one of the main problems.

The complicated and multifactorial nature of antimicrobial resistance is insufficiently investigated, especially in terms of interactions among people, animals and the environment. The absence of reliable information, slow development of new antimicrobial drugs and high indexes of diseases further worsen the situation. The appearance and spread of antimicrobial resistance demands immediate attention from both the medical staff and the developers of new compounds that may show antimicrobial activity [1].

According to that, the resistance of microorganisms to the drugs and disinfectants decreases the efficiency of the preventive measures and the treatment of human infectious diseases, that results in the increasing heaviness and the duration of these illnesses and the increasing mortality among the population. The World Health Organization (WHO) expects the resistance to antimicrobials to be the greatest threat to human health by 2050 [2]. For solving the described above problem, in order to provision the implementation of the National Security Strategy of the Russian Federation and the Fundamentals of State Policy in the field of ensuring chemical and biological security of the Russian Federation for the period up to 2025 and beyond in 2017 the Government of the Russian Federation approved the Strategy for preventing and overcoming the resistance of microorganisms and harmful plants to medicines, chemical and biological agents for the period up to 2030 and beyond [3]. Within this Strategy, the direction including the search for new methods of synthesizing substances that possess antimicrobial activity that may overcome the formed resistance mechanisms is implemented.

Previously diverse methods of oligohexamethyleneguanidine (OHMG) salts synthesizing were suggested

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which as shown [4] exposed sufficient efficiency against different pathogenic and opportunistic microorganisms also as fungi and viruses. That's why derivatives of oligohexamethyleneguanidine nowadays are actively used for creating drugs based on them.

The main problem in the process of obtaining the derivatives of poly- and oligohexamethyleneguanidine that concludes in the polycondensation of hexamethylenediamine (HMDA) and the guanidine salts with further conversion to the required OHMG salt is the rather high content of residual impurities. Recent research [5] shows that the use of microfluidic synthesis allows to achieve the low monomer impurity contents versus the bulk synthesis but the obtained results don't correspond to the requirements of the State Pharmacopoeia. The development of a purification process for OHMG derivatives is a highly complicated process that takes into account numerous factors. It is optimal for the implementation of this stage to use the tools of mathematical modeling [6–8]. For this reason, the aim of the article is the development of the purification stage of the substance oligohexamethyleneguanidine hydrocitrate (OHMG-HC) using multivariate analysis of multicriteria optimization.

2 Materials and methods

The oligohexamethyleneguanidine hydrocitrate (OHMG-HC) used as a raw material in this study was obtained from the Institute of Pharmaceutical Technology. All chemicals were of analytical purity. The chemicals needed for this research were chloroform (Merck EMSURE®, purity ≥99.8% CAS 67-66-3), carbon tetrachloride (Merck, purity ≥99.5% CAS 56-23-5), methylene chloride (Merck, purity ≥99.8%, CAS 75-09-2), acetone (Merck, purity ≥99.5%, CAS 67-64-1) were obtained from Chimmed.

The main methods of polymer purification consist of several cycles of dissolution with further precipitation and rinsing with diverse solvents [9]. For poly- and oligoguanidines [10], for example, chloroform, carbon tetrachloride are used as solvents. However, it's necessary to conduct numerous experiments with different variations and initial values combinations to detect the optimal purification time, components correlation, the dependence between the initial parameters and the quantity of residual impurities. This substantially increases the consumption of both reagents and time, which doesn't guarantee the quick obtaining of the satisfactory results. According to this, the instrument for improving the process parameters and resource saving is needed. Such a solution could be the use of mathematical modeling methods, namely, multifactorial analysis of multi-criteria optimization (MAMO) [11].

Therefore we suggested the following algorithmic sequence according to the MAMO methods:

1. Searching for information in foreign and native literary sources;
2. Carrying out preliminary experiments in case of the absence of reliable literature data;
3. Formulation of the theory of dependence of criteria on factors and definition of verifying parameters which confirm the theory validity;
4. Finding the approximating function according to step 3 based on the experimental data;
5. Searching for optimal values;
6. The conduction of checking experiments for accordance with the verification parameters that are specified in step 3;
7. Selection of the most appropriate ratio between time and solvent quantity from all the considered options.

In this paper the approaches to the application of the mathematical modelling due to above algorithmic sequence using the purification of the oligohexamethyleneguanidine hydrocitrate (OHMG-HC) as an example (Fig. 1).

Based on the literature data [12] the following solvents were chosen for the purification process: chloroform, carbon tetrachloride, methylene chloride, acetone. The most important and controlled factors are the quantity of added solvent and the time of sample settling in the chosen solvent.

The following indexes were chosen as the acceptable criterion for purpose-oriented product: the amount of related impurities – hexamethylenediamine (HMDA) and guanidine hydrocarbonate (GHC), sulfate ash, heavy metals, residual solvents (acetone, chloroform, methylene chloride, carbon tetrachloride). The appropriate data is taken from the State Pharmacopoeia of the Russian Federation XIV edition and is given in Table 1 [13–16].

Since there was no information about the mutual influence of factors, it is suggested that mutual influence is present, i.e. the dependence on the factors is nonlinear, namely, there may be quadratic addends, for example, *xy*. Therefore the experiments were planned according to the full factor design for range enlargement.

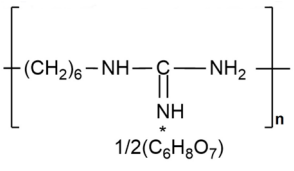


Fig. 1 The formula of OHMG hydrocitrate

Table 1 The quality measure for the purpose-oriented product

Index	Requirement for the residual impurities content (%)
Impurity of HMDA	No more than 0.05
Impurity of GHC	No more than 0.05
Sulfate ash [13, 14]	No more than 0.1
Heavy metals [15]	No more than 0.001
Chloroform [16]	No more than 0.006
Acetone [16]	No more than 0.5
Carbon tetrachloride [16]	No more than 0.0004
Methylene chloride [16]	No more than 0.06

Optimization using MAMO was carried out to check that the mutually influencing factors – time of settling (hours) and amount of solvent (ml), in our case, influenced the content of residual impurities.

The following step is to build the response surface (approximation). The dependence of criteria on factors, which corresponds to the full factorial design, has the form (here the addend *Dxy* corresponds to the mutual influence of factors) (Eq. (1)):

$$F(x, y) = A + Bx + Cy + Dxy, \quad (1)$$

where x is the solvent amount, y is the settling time and A, B, C, D are the regression coefficient.

According to the experimental data, it is possible to accurately determine the value of the coefficients A, B, C and D. The standard deviation for the $F(x, y)$ dependence is calculated, after that it is differentiated by each of the coefficients. The obtained system equates to zero and solves regarding the coefficients. Thus, an approximation of the dependence of the amount of each of the residual impurities on the normalized factors x, y is built. The approximative function graph is also known as the response surface.

The processing of experimental data and mathematical modeling by the method of multifactorial analysis of multicriteria optimization was carried out using Wolfram Mathematica software.

For verification of the hypothesis choice correctness the openness coefficient (R) will be used, it must be within the limits of 10% for checking experimental points [17]. The full factorial plan of the experiment is presented in Table 2. Within the chosen optimal way of purification, the relative standard deviation for the quality indexes of OHMG-HC (Table 1), that were obtained during the measurements of 5 samples, should be evaluated no more than 5%.

To purify the preparation, 10 ml of a 20% aqueous solution of OHMG-HC, followed by the addition of portions of the required amount of the solvent (Table 2). Mixtures selected to collect the aqueous and organic phases, the phase is decanted, and evaporation is carried out on a rotary evaporator at a temperature of 90–95 °C. The experiments were performed in two parallel measurements, the results described in this article represent the average of these measurements.

Table 2 Conditions for the purification process of the OHMG-HC salt

No. exp.	Solvent	Added amount of solvent (ml)	Time of settling (hours)
1	Chloroform	30	8
2		35	12
3		40	18
4		45	24
5	Carbon tetrachloride	30	8
6		35	16
7		40	24
8		45	28
9	Methylene chloride	30	16
10		35	24
11		40	28
12		45	36
13	Acetone	40	1.5
14		45	1
15		50	2
16		55	2.5

The concentration of HMDA and GHC was determined by chromatographic method of external standards with UV detection at wavelengths of 205 nm and 264 nm, respectively. Conditions for chromatographic determination of HMDA: column Luna C18(2) 5 μm, 150 × 4.6 mm; mobile phase A: water for chromatography; mobile phase B: acetonitrile; flow rate: 1 ml/min; temperature: 25 °C; volume of the injected sample: 20.0 μl; analysis time: 30 min; gradient profile: 0–3 min. 0% V, 4–15 min. 90% V, 16–30 min. 0% V. Conditions for the chromatographic determination of GHC: column Luna C18(2) 5 microns, 250 × 4.6 mm; mobile phase A: water for chromatography; liquid phase B: acetonitrile; flow rate: 1 ml/min; temperature: 30 °C; loop volume: 100 μl; gradient profile: 0–1 min. 40% V, 10–16 min. 90% V, 17–20 min. 40% V.

Determination of carbon tetrachloride, chloroform, methylene chloride and acetone are carried out using gas chromatography.

Conditions for chromatographic determination of chloroform and carbon tetrachloride: capillary column CR-5, length 30 m, inner diameter 0.32 mm and film thickness

0.5 μm, (Chromatek); evaporator temperature: 250 °C; detector temperature: 250 °C; carrier gas: nitrogen; the pressure of the carrier gas in the evaporator: 70 kPa; flow split: 1/50; detector type: electronic capture detector; liquid sample injection: 1.0 μl; temperature program of the column: 0–8 min: 40.0 °C; 8.0–11.6 min: 40.0→220.0 °C; 11.6-15.0 min 220.0 °C; approximate retention time: chloroform 2.7 min carbon tetrachloride 3.3 min.

Conditions for chromatographic determination acetone, methylene chloride: Phenomenex Zebron ZB-5 7HM-G002-17 capillary column, 30 m long, 0.32 mm inner diameter and 0.5 μm film thickness.

Evaporator temperature: 150 °C; detector temperature: 160 °C; carrier gas: nitrogen; the pressure of the carrier gas in the evaporator: 40 kPa; flow division: 1/80; detector type: flame ionization detector; equilibrium vapor input: 1.0 ml; temperature program of the column: 0–7 min: 50.0 °C, 7.0–12.0 min: 50.0→200.0 °C, 12.0–15.0 min: 200.0 °C; approximate retention time: acetone 2.5 min, methylene chloride 2.7 min.

3 Results and discussions

During the conducted preliminary experiments the following experimental data about the amount of impurities in the samples of OHMG-HC were obtained (Table 3).

To carry out the mathematical calculations it is necessary to accomplish the non-dimensionalization (normalization) of the obtained data. The information about the amount of solvents (x) and time of mixture settling (y) are normalized in accordance with the following formula (Eq. (2)):

$$x_{norm} = \frac{x - x_{\min}}{x_{\max} - x_{\min}}, \quad y_{norm} = \frac{y - y_{\min}}{y_{\max} - y_{\min}}, \tag{2}$$

The facts about the residual impurities (z) are normalized so (Eq. (3)) that the value of 0 matches with the actual value of 0, and that the value of 1 corresponds to the limited permissible concentration, (thus in the graphs everything below the line $y = 1$ is acceptable):

$$z_{norm} = \frac{z}{z_{\text{limited permissible}}}. \tag{3}$$

The normalized information is presented in Table 4.

3.1 Carbon tetrachloride

For carbon tetrachloride, dependences (F) of impurities on the amount of added solvent (x) and time (y) were obtained (Eqs. (4)–(8)), (Fig. 1 shows the response surface, $\max(F_{\text{solvent}}, F_{\text{HMDA}}, F_{\text{GHC}}, F_{\text{sulfuric ash}}, F_{\text{heavy metals}})(x, y)$). The optimal points should be located in the area of light blue color, i.e. in the range [0, 1] along the z-axis). If there is no such area, then the surface along the z-axis is above the value 1, so there are no optimal points for the solvent (Fig. 2).

Table 3 Conditions for the purification process of the OHMG-HC salt

No.	Solvent	Amount after purification, %	Impurity of HMDA, %	Impurity of GHC, %	Sulfate ash, %	Heavy metals, %
1	Chloroform	0.014	0.242	0.125	0.03	0.0007
2		0.008	0.108	0.076	0.01	0.0009
3		0.018	0.074	0.048	0.04	0.0011
4		0.007	0.056	0.062	0.02	0.0009
5	Carbon tetrachloride	0.042	0.350	0.09	0.07	0.0008
6		0.053	0.239	0.312	0.04	0.0012
7		0.078	0.320	0.222	0.03	0.0010
8		0.062	0.159	0.190	0.11	0.0012
9	Methylene chloride	0.142	0.136	0.173	0.03	0.0007
10		0.099	0.142	0.059	0.02	0.0012
11		0.068	0.110	0.051	0.06	0.0009
12		0.055	0.091	0.047	0.09	0.0034
13	Acetone	0.093	0.092	0.039	0.02	0.0006
14		0.017	0.043	0.044	0.04	0.0008
15		0.009	0.050	0.051	0.03	0.0009
16		0.012	0.049	0.046	0.03	0.0005

Table 4 The normalized experimental data

No.	Solvent	Normalized added volume OHMG-HC	Normalized settling time
1	Chloroform	0.67	0.33
2		0.78	0.50
3		0.89	0.75
4		1.00	1.00
5	Carbon tetrachloride	0.67	0.26
6		0.78	0.57
7		0.89	0.86
8		1.00	1.00
9	Methylene chloride	0.67	0.44
10		0.78	0.67
11		0.89	0.78
12		1.00	1.00
13	Acetone	0.73	0.60
14		0.82	0.40
15		0.91	0.80
16		1.00	1.00

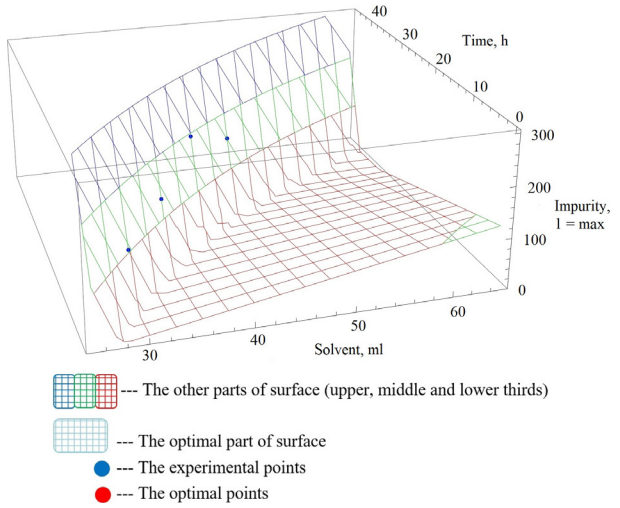


Fig. 2 The results of optimization OHMG-HC with carbon tetrachloride

$$F_{\text{solvent}}(x,y)=\begin{pmatrix}1262.5-2070x+\\411.25y+551.25xy\end{pmatrix}\times 0.0004\% \quad (4)$$

$$F_{\text{HMDA}}(x,y)=\begin{pmatrix}101.36-158.94x\\+0.28y+60.48xy\end{pmatrix}\times 0.05\% \quad (5)$$

$$F_{\text{GHC}}(x,y)=\begin{pmatrix}-89.48+145.08x\\+46.48y-98.28xy\end{pmatrix}\times 0.05\% \quad (6)$$

$$F_{\text{sulfuric ash}}(x,y)=\begin{pmatrix}-4.8+10.8x\\-8.05y+3.15xy\end{pmatrix}\times 0.1 \quad (7)$$

$$F_{\text{heavy metals}}(x,y)=\begin{pmatrix}-10.7+18.9x\\+2.45y-9.45xy\end{pmatrix}\times 0.001\% \quad (8)$$

As we can see in Fig. 2, the amount of impurities after cleaning is too large and exceeds the maximum allowable value (there should be a light blue suitable area somewhere inside red, but in fact there is no one).

3.2 Methylene chloride

For methylene chloride, dependences (F) of the impurity on the amount of added solvent (x) and time (y) were obtained (Eqs. (9)–(13)), (Fig. 3 shows the response surface, $\max(F_{\text{solvent}}, F_{\text{HMDA}}, F_{\text{GHC}}, F_{\text{sulfuric ash}}, F_{\text{heavy metals}})(x,y)$). The optimal points should be located in the area of light blue color, i.e. in the range [0, 1] along the z-axis). If there is no such area, then the surface along the z-axis is above the value 1, so there are no solvent optimal points (Fig. 3).

$$F_{\text{solvent}}(x,y)=\begin{pmatrix}8.78-9.28x\\-4.37y+5.79xy\end{pmatrix}\times 0.06\% \quad (9)$$

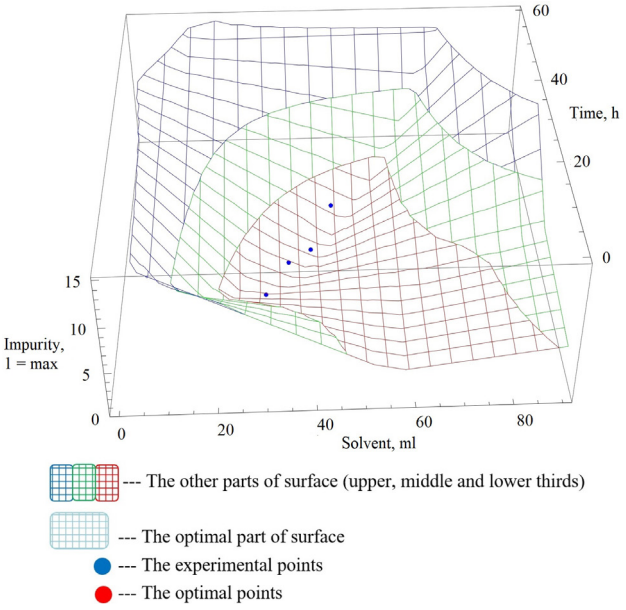


Fig. 3 The results of optimization OHMG-HC with methylene chloride

$$F_{\text{HMDA}}(x,y)=\begin{pmatrix}4.39-6.17x\\+9.41y-5.79xy\end{pmatrix}\times 0.05\% \quad (10)$$

$$F_{\text{GHC}}(x,y)=\begin{pmatrix}16.52-10.65x\\-30.39y+25.46xy\end{pmatrix}\times 0.05\% \quad (11)$$

$$F_{\text{sulfuric ash}}(x,y)=\begin{pmatrix}-0.13+2.96x\\-6.56y+4.63xy\end{pmatrix}\times 0.1\% \quad (12)$$

$$F_{\text{heavy metals}}(x,y)=\begin{pmatrix}18.96-35.61x\\-3.09y+23.14xy\end{pmatrix}\times 0.001\% \quad (13)$$

As we can see in Fig. 3, the amount of impurities after cleaning is too large and exceeds the maximum allowable value (there should be a light blue suitable area somewhere inside red, but in fact there is no one).

3.3 Chloroform

For chloroform, dependences (F) of the impurity on the amount of added solvent (x) and time (y) were obtained (Eqs. (14)–(18)), (Fig. 4 shows the response surface, $\max(F_{\text{solvent}}, F_{\text{HMDA}}, F_{\text{GHC}}, F_{\text{sulfuric ash}}, F_{\text{heavy metals}})(x,y)$). The optimal points should be located in the area of light blue color, i.e. in the range [0, 1] along the z-axis). If there is no such area, then the surface along the z-axis is above the value 1, so there are no optimal points for this solvent (Fig. 4).

$$F_{\text{solvent}}(x,y)=\begin{pmatrix}36.67-88.5x\\+116y-63xy\end{pmatrix}\times 0.006\% \quad (14)$$

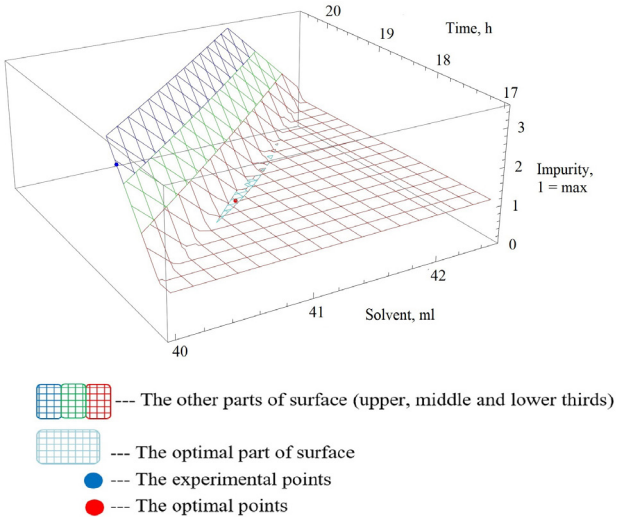


Fig. 4 The results of optimization OHMG-HC with chloroform

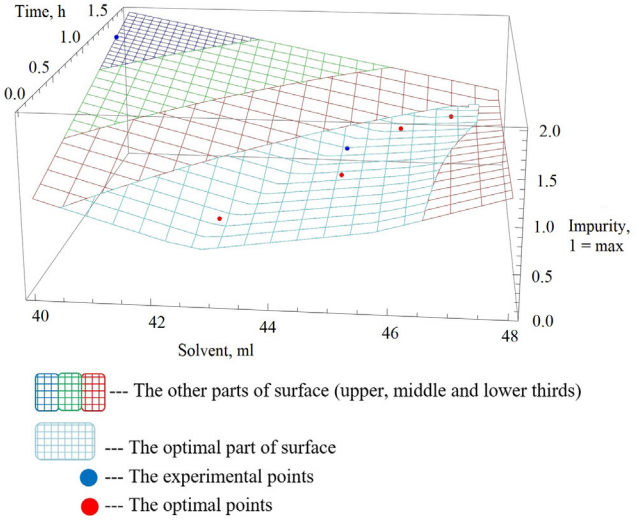


Fig. 5 The results of optimization OHMG-HC with acetone

$$F_{\text{HMDA}}(x,y)=\begin{pmatrix}36.28-57.24x\\+16.32y+5.76xy\end{pmatrix}\times 0.05\% \quad (15)$$

$$F_{\text{GHC}}(x,y)=\begin{pmatrix}10.06-8.82x\\-15.12y+15.12xy\end{pmatrix}\times 0.05\% \quad (16)$$

$$F_{\text{sulfuric ash}}(x,y)=\begin{pmatrix}6.5-15.3x\\+18y-9xy\end{pmatrix}\times 0.1\% \quad (17)$$

$$F_{\text{heavy metals}}(x,y)=\begin{pmatrix}0.3-1.8x\\+9.6y-7.2xy\end{pmatrix}\times 0.001\% \quad (18)$$

As can be seen from Fig. 4, with the required ratio of the amount of solvent and time, the amount of residue after cleaning can be below the maximum allowable values. This area is marked in light blue in Fig. 4 (inside the red area). In this allowable area, the optimal point for the reaction was found (red dot on the graph) with integer values of the added amount of solvent and time are 41 ml and 18 h 20 min respectively.

3.4 Acetone

For acetone, dependences (F) of the impurity on the amount of added solvent (x) and time (y) were obtained (Eqs. (19)–(23)), (Fig. 5 shows the response surface, max(F_{solvent}, F_{HMDA}, F_{GHC}, $F_{\text{sulfuric ash}}$, $F_{\text{heavy metals}}$) (x, y)). The optimal points should be located in the area of light blue color, i.e. in the range [0, 1] along the z-axis). If there is no such area, then the surface along the z-axis is above the value 1, so there are no optimal points for solvent (Fig. 5).

$$F_{\text{solvent}}(x,y)=\begin{pmatrix}1.79-2.23x\\-1.12y+1.59xy\end{pmatrix}\times 0.5\% \quad (19)$$

$$F_{\text{HMDA}}(x,y)=\begin{pmatrix}8.38-10.03x\\-2.4y+5.03xy\end{pmatrix}\times 0.05\% \quad (20)$$

$$F_{\text{GHC}}(x,y)=\begin{pmatrix}-3.15+4.81x\\+4.6y-5.34xy\end{pmatrix}\times 0.05\% \quad (21)$$

$$F_{\text{sulfuric ash}}(x,y)=(-0.3+1.1x-0.5y)\times 0.1\% \quad (22)$$

$$F_{\text{heavy metals}}(x,y)=\begin{pmatrix}-7.64+10.21x\\+10.5y-12.57xy\end{pmatrix}\times 0.001\% \quad (23)$$

As we can see from the graphs (Fig. 5) of residual impurities, acetone is the best solvent because it demands less settling time in comparison to chloroform, carbon tetrachloride and methylene chloride.

In case of purification with chloroform (Fig. 4) and acetone (Fig. 5), for those points which meet the criteria the values of the acceptance criteria were calculated (Table 5).

The data obtained by the multifactorial analysis of multi-criteria optimization shows that the suggested optimal point for hydrocitrate OHMG for the chloroform solvent is situated on the border of the acceptance criteria in terms of impurities of GHC and heavy metals. Also, the proposed optimal points for the acetone solvent in the ratios of 46 ml–75 min and 47 ml–85 min are situated on the border of the acceptance criteria in terms of impurities of GHC, HMDA and heavy metals. According to that the most optimal way of purification of OHMG hydrocitrate is reprecipitation with acetone at the ratio of the added solvent and the settling time of the mixture given in Table 6.

After carrying out the mathematical calculations, it was decided to reproduce the control experiments that

Table 5 The values of the acceptance criteria in optimal points for purification of OHMG-HC with chloroform and acetone

Solvent	The amount of solvent and mixture settling time	The amount of solvent after purification (%)	The impurity of HMDA (%)	The impurity of GHC (%)	The sulfuric ash (%)	Heavy metals (%)
Chloroform	41 ml, 18 h 20 min	0.005	0.030	0.049	0.005	0.0009
Acetone	43 ml, 15 min	0.030	0.035	0.032	0.051	0.0004
	45 ml, 40 min	0.005	0.032	0.042	0.048	0.0008
	46 ml, 75 min	0.013	0.045	0.047	0.037	0.0009
	47 ml, 85 min	0.008	0.044	0.049	0.035	0.0009

Table 6 Optimal parameters of the purification process of the OHMG-HC salt

No.	The amount of added solvent (x) (ml)	Time (y) (min)
1	43	15
2	45	40

may check the correctness of the obtained data (optimal points). The obtained experimental data are presented in Table 7. In Fig. 6 the results of HPLC analysis for the content of impurities in samples No. 1–2 of OHMG-HC of acetone (a), HMDA (b), and GHC (c) are shown.

Thus, based on a comparison of the experimental data with the data obtained using MAMO, we can conclude that

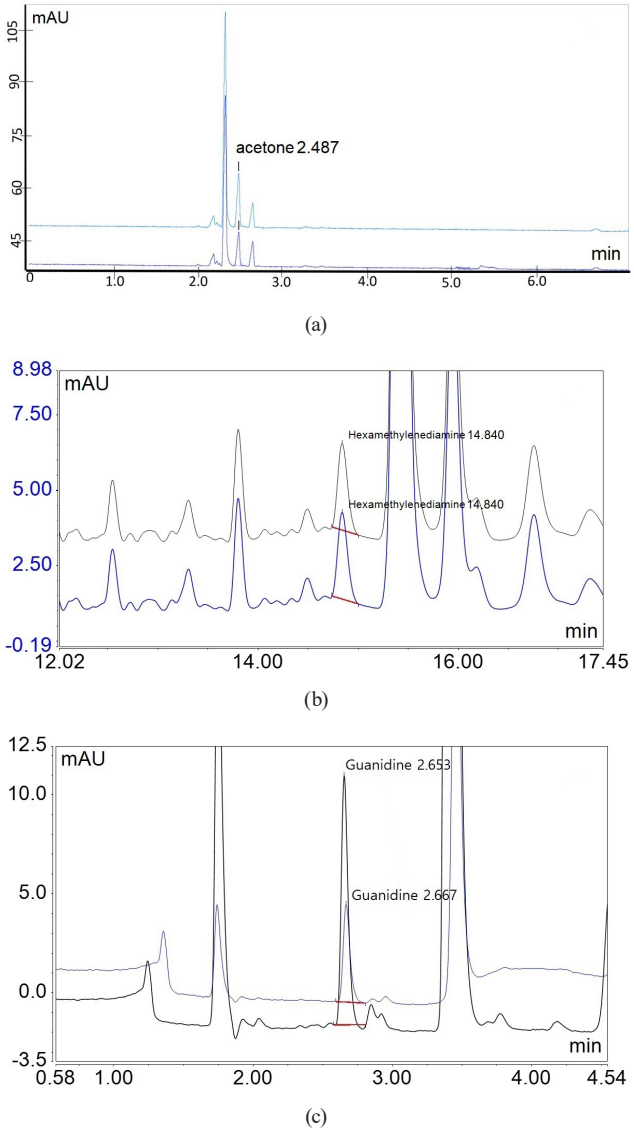


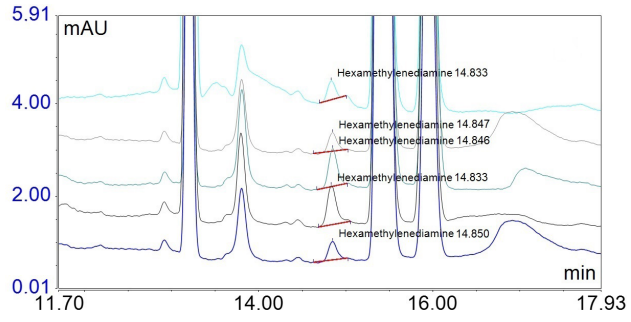
Fig. 6 The results of HPLC analysis for the content of impurities of acetone (a), HMDA (b), and GHC (c) for the samples No. 1–2 of OHMG-HC

Table 7 The experimental and mathematically obtained data

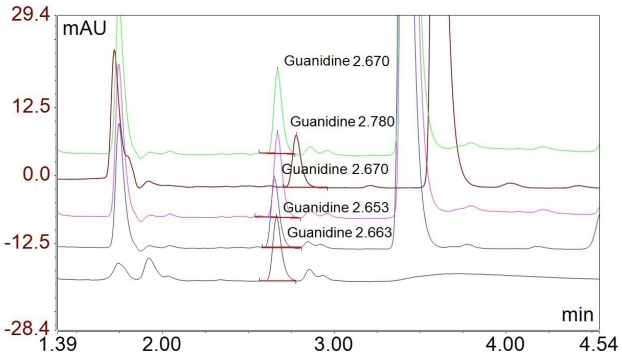
No. sample	1	2	
The amount of added solvent (ml)	43	45	Coefficient R, theoretical/practical
Mixture setting time (min)	15	40	
The amount of solvent after purification theoretical (%)	0.03	0.005	102.90%
The amount of solvent after purification practical (%)	0.021	0.013	
HMDA theoretical (%)	0.035	0.032	103.10%
HMDA practical (%)	0.032	0.033	
GHC theoretical (%)	0.032	0.042	102.80%
GHC practical (%)	0.029	0.043	
Sulfuric ash theoretical (%)	0.051	0.048	105.3%
Sulfuric ash practical (%)	0.045	0.049	
Heavy metals theoretical (%)	0.0004	0.0008	92.305%
Heavy metals practical (%)	0.0005	0.0008	

the hypothesis was chosen correctly, because for quantitative determination methods, the openness rate (*R*) corresponds to the interval from 90% to 110%.

As another verification parameter, an assessment of convergence (repeatability) was carried out. For OHMG-HC was selected at the proposed optimal point, 5 experiments were carried out on different series of salts OHMG-HC (the results of HPLC analysis are presented in Fig. 7), the standard deviation and dispersion were calculated for the results of impurities of HMDA, GHC, sulfate ash and heavy metals (Table 8).



(a)



(b)

Fig. 7 The HPLC analysis results for HMDA (a) and GHC (b) impurities for OHMG-HC obtained for the convergence study (5 replicates)

The characteristics presented in Table 1 indicate the compliance of the obtained results with the established acceptance criteria and the reproducibility of the technological stage of purification of OHMG-HC under the conditions selected using MAMO.

4 Conclusion

The obtained results were interpreted using multifactorial analysis of multi-criteria optimization (MAMO) according to the previously described algorithm. As a result, the dependencies of the influence of the ratio of the added amount of solvent and the mixture settling time on the final content of impurities in the purpose-oriented product were revealed. It was found that for the maximum qualitative purification of OHMG hydrocitrate, it is reasonable to use acetone, because the process time is reduced to several hours, while the amount of impurities is minimal. Also, the correctness and repeatability of the suggested algorithmic model was substantiated with the statistical methods. The use of mathematical methods, in particular MAMO, for predicting the results and plotting the dependences of the parameters and the criteria of reaction, confirmed the reasonability of their use, as it reduces the time and material costs of experiments.

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Table 8 The results of testing the method for convergence

No.	The purification conditions		The quality criteria			
	The volume of added solvent (ml)	The settling time (min)	HMDA (%)	GHC (%)	Sulfuric ash (%)	Heavy metals (%)
1	45	40	0.028	0.038	0.049	0.0008
2			0.031	0.037	0.041	0.0006
3			0.034	0.039	0.045	0.0005
4			0.028	0.040	0.043	0.0006
5			0.030	0.039	0.047	0.0007
	$\bar{A} \pm \sigma$		0.030 ± 0.002	0.039 ± 0.002	0.045 ± 0.003	0.0006 ± 0.0001

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