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Original Article

# OPTIMIZATION OF THE TECHNOLOGY FOR PRODUCING A MAGNETO CONTROLLABLE NANOCOMPOSITE Ag@$Fe_3O_4$ USING MATHEMATICAL DESIGN

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ABSTRACT

**Objective:** The purpose of the research was to optimize technology for producing a magneto controllable nanocomposite Ag@$Fe_3O_4$ with modern physicochemical and therapeutic requirements using methods of mathematical design of the experiment.

**Methods:** To optimize the synthesis process of the nanocomposite Ag@$Fe_3O_4$, the method of factor experiment was used. Mathematical calculations were performed using the STATISTICA 10 StatSoft Inc. system and Excel spreadsheet processor of MS Office 2019 Professional Plus.

**Results:** Based on the study of technological parameters of nanocomposite synthesis Ag@$Fe_3O_4$ (16 experiments) a regression equation was obtained: $Y = 106.415+0.038X_1+4.448X_2+1.806X_3-1.593X_4-18.945X_5-109.980X_6$. By the use of this equation the synthesis parameters were optimized with the help of steepest ascent method. It was found that the maximum yield of Ag@$Fe_3O_4$ can be achieved under the following conditions: $X_1$ (magnetite synthesis time, min)–40; $X_2$ (glucose content in solution, %)–10; $X_3$ (temperature of the Tollens reaction, °C)–65; $X_4$ (magnetite silver coating time, min)–30; $X_5$ (pH, units)–8.5; $X_6$ (rate of addition of ammonia, mol/min)–0.36.

**Conclusion:** Using mathematical design of the experiment, a technology was developed for producing Ag@$Fe_3O_4$ with modern physicochemical and therapeutic requirements.

**Keywords**: Synthesis, Technology, Nanoparticles, Silver shell, Magneto controllable composite system, Methods of mathematical design, Regression and correlation analysis, Response surface methodology


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## INTRODUCTION

One of the main tasks of pharmaceutical science is the development of effective methods of treatment, diagnosis and prevention, creation of highly effective drugs. Thanks to nanotechnology, at the intersection of various branches of science and technology, new nanomaterials with unique properties were created and studied [1], the main structural element of which is a nanoscale magneto controllable particle (magnetite, $Fe_3O_4$) [2] with a surface modified by various therapeutic agents or noble metals [3].

The basis for obtaining multifunctional drugs [4] with directed action is to study the mechanisms of formation of the surface layer on magnetite, which is accompanied by the selection of the optimal amount of modifying agent. This involves the development of a simple rational synthesis method that provides more precise control of the process itself. So, it is possible to obtain $Fe_3O_4$ nanoparticles of a certain size, to deposit a modifying agent on their surface with a layer of the required thickness and area, without compromising the magnetic characteristics of the modified composite.

Formation of Ag@$Fe_3O_4$ composite structures of the "core-shell" type where the core is magnetite and the shell is a chemically inert biocompatible metal (Ag) allows combining the benefits of magnetic properties of the core with bactericidal and bacteriostatic properties of the shell. It is promising for the further use in pharmacy and medicine [5]. Therefore, it is important to observe its purity, basic physicochemical characteristics and reproducibility of the results, as well as the maximum yield of the target product.

Owing to mentioned facts, firstly in this study the technology for producing a magneto controllable Ag@$Fe_3O_4$ nanocomposite with modern physicochemical and therapeutic requirements was optimized using the methods of mathematical design of the experiment.

The realization of this purpose required the following tasks: 1) to determine the conditions for the synthesis of magnetite core (experiment duration, rate of ammonia addition, temperature regimen); 2) achieve the required ratio of core: shell by selection (concentration of reducing agent (glucose), the duration of the silver coating on magnetite, optimal pH of the reaction mixture); 3) to develop conditions for the production of a magneto controllable Ag@$Fe_3O_4$ nanocomposite with an optimal yield.

In order to optimize technological processes, mathematical methods of experiment planning were used to prevent unnecessary costs associated with production. So, it made it more efficient, economical and profitable. Nowadays there are several approaches to the mathematical study of unknown phenomena in scientific research [6–9].

The use of active experiment methods allowed to obtain mathematical models describing the properties of objects of research, in which there was no need to evaluate the processes taking place inside the object. Obtaining a mathematical model is ensured by a clear implementation of the research algorithm and determining the values of the response function of the object [10].

The design of the experiment made possible to simultaneously vary all factors and obtain quantitative estimates of both the main factors and the effects of the interaction between them. Moreover, obtained results are characterized by a smaller error than traditional methods of one-pot research [11, 12].

## MATERIALS AND METHODS

### Synthesis of Ag@$Fe_3O_4$ samples

Method of synthesis was published earlier [5, 13].

### Mathematical design

Mathematical calculations were performed using the STATISTICA 10 StatSoft Inc. system and Excel spreadsheet processor of MS Office 2019 Professional Plus.

## RESULTS AND DISCUSSION

16 samples of the nanocomposite $Ag@Fe_3O_4$ was obtained; the main characteristics of which were established by modern physicochemical methods [5; 13, 14].

With a large number of independent technological factors, it was necessary to search in what combination of the factors the yield of $Ag@Fe_3O_4$ would be maximum. To solve this problem, the regression patterns obtained during the planning of the experiment were used.

In this regard, in order to optimize the environment, it was advisable, in our opinion, to use the factor experiment method, which makes it possible to carry out a large number of experiments, realize possible combinations of the main levels of independent variable factors, establish their optimal levels. It was also much faster than the empirical method to find and justify the optimal technological parameters.

According to the results of an experiment of optimization of process of producing $Ag@Fe_3O_4$ using the steepest ascent method, combining the design of the experiment with the gradient-based path optimization method [15], it was experimentally found that six factors influenced the output of $Ag@Fe_3O_4$ (Y): synthesis time of magnetite core, min ($X_1$); glucose concentration in solution,% ($X_2$); Tollens reaction temperature, °C ($X_3$); silver coating time of magnetite, min ($X_4$); pH of the reaction mixture, units ($X_5$); the rate of addition of ammonia, mol/min ($X_6$) (table 1).

**Table 1: Experiment parameters of the synthesis of nanocomposite $Ag@Fe_3O_4$[a]**

| № | $X_1$ (min) | $X_2$ (%) | $X_3$ (°C) | $X_4$ (min) | $X_5$ (units) | $X_6$ (mol/min) | Y (%) |
|---|---|---|---|---|---|---|---|
| 1 | 20 | 5 | 45 | 20 | 8.0 | 0.18 | 55 |
| 2 | 25 | 6 | 50 | 22 | 8.5 | 0.20 | 62 |
| 3 | 30 | 7 | 55 | 24 | 8.5 | 0.22 | 65 |
| 4 | 35 | 8 | 60 | 26 | 8.5 | 0.24 | 72 |
| 5 | 40 | 9 | 65 | 28 | 9.0 | 0.26 | 75 |
| 6 | 45 | 10 | 70 | 30 | 9.5 | 0.28 | 76 |
| 7 | 50 | 11 | 75 | 32 | 10.0 | 0.30 | 79 |
| 8 | 40 | 10 | 65 | 30 | 9.0 | 0.34 | 82 |
| 9 | 50 | 9 | 70 | 32 | 8.0 | 0.38 | 80 |
| 10 | 30 | 6 | 75 | 34 | 8.5 | 0.40 | 69 |
| 11 | 20 | 8 | 80 | 36 | 9.0 | 0.42 | 65 |
| 12 | 60 | 7 | 85 | 38 | 9.5 | 0.44 | 59 |
| 13 | 45 | 12 | 70 | 40 | 9.0 | 0.48 | 57 |
| 14 | 50 | 13 | 60 | 26 | 10.0 | 0.50 | 45 |
| 15 | 40 | 14 | 65 | 28 | 10.5 | 0.52 | 42 |
| 16 | 60 | 15 | 85 | 40 | 11 | 0.54 | 40 |

[a]$X_1$–magnetite synthesis time, min; $X_2$–glucose concentration in solution, %; $X_3$–Tollens reaction temperature, °C; $X_4$–silver coating time of magnetite, min; $X_5$–pH of the reaction mixture, units; $X_6$–rate of addition of ammonia, mol/min; Y–yield of nanocomposite $Ag@Fe_3O_4$, %.

The process of statistical processing of the results of experimental studies was divided into two stages: 1) study of the relationship between the yield of the nanocomposite $Ag@Fe_3O_4$ (dependent variable Y) and the independent variables ($X_1$–$X_6$) (table 1) with the determination of the correspondence of the selected linear model to the experimental results; 2) a search for optimal conditions for the production of the nanocomposite $Ag@Fe_3O_4$.

During the experiment, the parameters $X_1$–$X_6$ were checked in order to determine the most significant among them.

To construct a mathematical model, a factor experiment has been carried out in which the yield parameter of the nanocomposite $Ag@Fe_3O_4$ (Y, %) was the optimization parameter (dependent factor), and $X_1$-$X_6$ were independent factors.

When planning according to this scheme, the upper and lower levels were established experimentally. Based on the average values of the parameters $X_1$–$X_6$, the center of the plan and the step of variation were determined.

Verification showed that the experimental data were normally distributed and homogeneous.

To construct and analyze empirical models in the experiment, the following criteria were used: selection and optimization of the model, and also the assessment of the results.

The calculation according to the choice of the model was carried out according to the linear dependence formula, which is the hyperplane equation in the space of *n*-parameters of independent $x_j$:

$$y = b_0 + \sum_{j=1}^{m} b_j x_j$$

Where $b_j$–coefficients for unknown; $b_0$–free term.

To select the parameters of the system $b_0$, $b_j$ in order to optimize the model, linear estimation was used, as well as regression analysis [16].

These calculations were performed according to the experimental data using the STATISTICA 10 StatSoft Inc. system [17, 18], on the basis of which the regression equation was received for the process of producing of the nanocomposite $Ag@Fe_3O_4$ (fig. 1).

| Effect | Y Param. | Y Std.Err | Y t | Y p | -80,00% Cnf.Lmt | +80,00% Cnf.Lmt | Y Beta (Я) | Y St.Err.Я | -80,00% Cnf.Lmt | +80,00% Cnf.Lmt |
|---|---|---|---|---|---|---|---|---|---|---|
| Intercept | 160,415 | 32,65011 | 4,91316 | 0,000832 | 115,259 | 205,5713 | | | | |
| X1 | 0,038 | 0,22915 | 0,16557 | 0,872156 | -0,279 | 0,3549 | 0,03550 | 0,214426 | -0,26106 | 0,332060 |
| X2 | 4,448 | 1,60899 | 2,76440 | 0,021954 | 2,223 | 6,6731 | 0,98254 | 0,355426 | 0,49097 | 1,474104 |
| X3 | 1,806 | 0,57246 | 3,15460 | 0,011651 | 1,014 | 2,5976 | 1,54200 | 0,488808 | 0,86596 | 2,218032 |
| X4 | -1,593 | 1,04661 | -1,52188 | 0,162367 | -3,040 | -0,1453 | -0,72109 | 0,473812 | -1,37638 | -0,065790 |
| X5 | -18,945 | 5,26674 | -3,59708 | 0,005775 | -26,229 | -11,6608 | -1,21961 | 0,339055 | -1,68853 | -0,750684 |
| X6 | -109,980 | 30,86408 | -3,56338 | 0,006087 | -152,666 | -67,2944 | -0,97672 | 0,274098 | -1,35580 | -0,597630 |

**Fig. 1: The results of the calculation of regression coefficients**

As a result of the calculation, the following regression equation was obtained:

$$Y = 106.415+0.038X_1+4.448X_2+1.806X_3-1.593X_4-18.945X_5-109.980X_6$$

Coefficients of interaction between factors (excess effects) were not taken into account, since they were linear combinations of other effects and cannot be estimated.

The significance of the regression coefficients was checked by Student's criterion. The variance of reproducibility of the regression coefficients was 2245.001, the variance error was 495.936 (fig. 2).

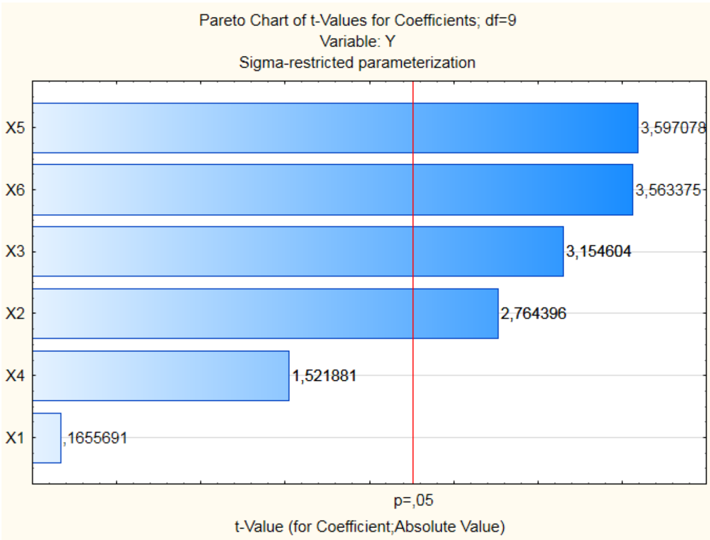
The calculation method established that for the confidence probability P = 0.95, 4 variables were significant–pH ($X_5$), the rate of addition of ammonia ($X_6$), Tollens reaction temperature ($X_3$), glucose concentration in solution ($X_2$) (fig. 3, A). For the confidence probability *P* = 0.8 5 variables were significant (in descending order): $X_5$ (pH, units)>$X_6$ (the rate of addition of ammonia, mol/min)>$X_3$ (Tollens reaction temperature, °C)>$X_2$ (glucose concentration in solution, %)>$X_4$ (silver coating time of magnetite, min)>$X_1$ (synthesis time of magnetite core, min) (fig. 3, B).

Model assessment: in general, the multiple correlation R = 0.819 is quite strong (fig. 2); the significance of the coefficients in the variables $X_1$–$X_6$ is shown (fig. 3); in the table of residuals the degree of accordance of the model in this experiment is visible (fig. 4).

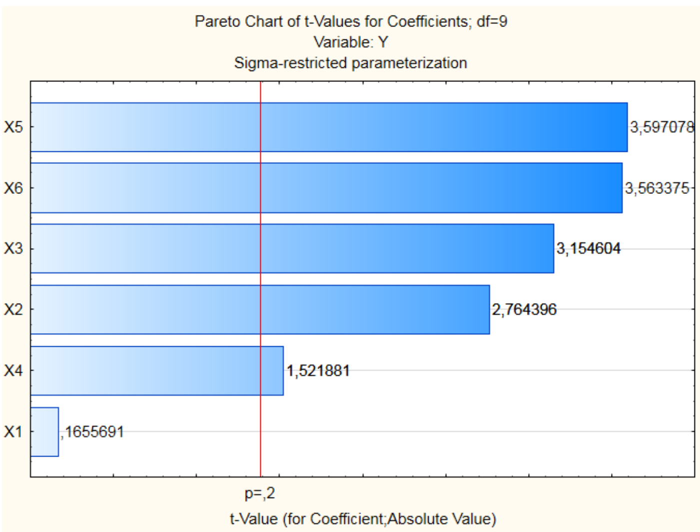
The assessment of adequacy of the adopted model (linearity) was performed using the Fisher criterion (F), the calculated value of which was 6.790 (fig. 2), and the literary value F* = 2.538, which corresponds to the probability P (F*) = 0.95. Therefore, the equation regression was adequate.

| | Test of SS Whole Model vs. SS Residual (Synth. Ag-Fe3O4 Experimental Data.sta) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Dependnt Variable | Multiple R | Multiple RI | Adjusted RI | SS Model | df Model | MS Model | SS Residual | df Residual | MS Residual | F | p |
| Y | 0,905021 | 0,819063 | 0,698439 | 2245,001 | 6 | 374,1669 | 495,9360 | 9 | 55,10400 | 6,790195 | 0,005921 |

**Fig. 2: Verification of the significance of regression coefficients**




**A**




**B**

**Fig. 3: Pareto diagrams of independent factors $X_1$–$X_6$ for confidence probability P = 0.95 (A) and P = 0.8 (B)**

| Case number | Observed, Predicted, and Residual Values Sigma-restricted parameterization (Analysis sample) Y Observed | Y Predictd | Y Resids |
|---|---|---|---|
| 1 | 55,00000 | 61,46591 | -6,4659 |
| 2 | 62,00000 | 60,27518 | 1,7248 |
| 3 | 65,00000 | 68,55689 | -3,5569 |
| 4 | 72,00000 | 76,83861 | -4,8386 |
| 5 | 75,00000 | 75,64787 | -0,6479 |
| 6 | 76,00000 | 74,45714 | 1,5429 |
| 7 | 79,00000 | 73,26641 | 5,7336 |
| 8 | 82,00000 | 68,11170 | 13,8883 |
| 9 | 80,00000 | 84,43265 | -4,4326 |
| 10 | 69,00000 | 64,50191 | 4,4981 |
| 11 | 65,00000 | 67,18995 | -2,1899 |
| 12 | 59,00000 | 58,43138 | 0,5686 |
| 13 | 57,00000 | 54,90113 | 2,0989 |
| 14 | 45,00000 | 42,63487 | 2,3651 |
| 15 | 42,00000 | 40,87503 | 1,1250 |
| 16 | 40,00000 | 51,41338 | -11,4134 |

**Fig. 4: Observed and predicted values and residuals**

**Establishment of optimal technological parameters of producing of nanocomposite Ag@$Fe_3O_4$**

According to the mentioned data, the optimization of the process of producing the nanocomposite Ag@$Fe_3O_4$ represented a targeted search for the values of influencing factors for which the extremum of the optimality criterion was reached (taking into account the restrictions imposed on all the influencing factors and response functions). The solution of the tasks depended on changes of independent and dependent variables; search start points and type of regression equation.

In the planned experiments, it was required to achieve the optimum yield of the Ag@$Fe_3O_4$ nanocomposite under the following restrictions on the main technological parameters determined experimentally: $20 \le X_1 \le 60$ min; $5 \le X_2 \le 15$ %; $45 \le X_3 \le 85$ °C; $20 \le X_4 \le 40$ min; $8 \le X_5 \le 11$ units; $0.18 \le X_1 \le 0.54$ mol/min (fig. 5, table 2).

| Variable | Descriptive Statistics (Synth. Ag-Fe3O4 Experimental Data.sta) Valid N | Mean | Minimum | Maximum | Std.Dev. |
|---|---|---|---|---|---|
| X1 | 16 | 40,00000 | 20,00000 | 60,00000 | 12,64911 |
| X2 | 16 | 9,37500 | 5,00000 | 15,00000 | 2,98608 |
| X3 | 16 | 67,18750 | 45,00000 | 85,00000 | 11,54249 |
| X4 | 16 | 30,37500 | 20,00000 | 40,00000 | 6,11964 |
| X5 | 16 | 9,15625 | 8,00000 | 11,00000 | 0,87023 |
| X6 | 16 | 0,35625 | 0,18000 | 0,54000 | 0,12005 |

**Fig. 5: Restrictions of dependent factors according to the results of calculations using the STATISTICA 10 soft**

**Table 2: Data for calculations to optimize the conditions for obtaining Ag@$Fe_3O_4$**

| Factors | Restrictions of factors | Mean | Regression coefficient[a], $b_i$ |
|---|---|---|---|
| $X_1$ | 20 ÷ 60 | 40.000 | 0.038 |
| $X_2$ | 5 ÷ 15 | 9.375 | 4.448 |
| $X_3$ | 45 ÷ 85 | 67.188 | 1.806 |
| $X_4$ | 20 ÷ 40 | 30.375 | −1.593 |
| $X_5$ | 8 ÷ 11 | 9.156 | −18.945 |
| $X_6$ | 0.18 ÷ 0.54 | 0.356 | −109.980 |

[a]$b_0$ = 160.415

The use of the simplex method to solve the obtained regression equation (using MS Excel 2019, MathCad 14), taking into account the limitations of the factors (table 2), did not give satisfactory results.

Based on the results of the experiment, we can suppose that for further optimization of the synthesis parameters, the use of the steepest ascent method will be effective, because the obtained linear model is adequate and is not too asymmetric with respect to the coefficients. The calculations were performed using the Excel table processor of MS Office 2019 Professional Plus soft (Ver. 1905) [18].

As a result, with a help of steepest ascent method, the optimal conditions for the synthesis technology of the Ag@$Fe_3O_4$ nanocomposite were determined. The maximum yield of the target product can be achieved under the following conditions: $X_1$ (magnetite synthesis time, min) 40; $X_2$ (glucose concentration in solution, %) 10; $X_3$ (Tollens reaction temperature, °C) 65; $X_4$ (silver coating time of magnetite, min) 30; $X_5$ (pH, units) 8.5; $X_6$ (rate of addition of ammonia, mol/min) 0.36.

## CONCLUSION

Using mathematical design of the experiment, a technology was developed for producing a magneto controllable nanocomposite $Ag@Fe_3O_4$ with modern physicochemical and therapeutic requirements.

## FUNDING

Nil

## AUTHORS CONTRIBUTIONS

All the authors contributed equally.

## CONFLICTS OF INTERESTS

Declared none

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