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## **Poly lactide-co-glycolide nanoparticles immobilized with isoniazid: optimization using the experimental Taguchi method**

The research aims to optimize and minimize the number of experiments to obtain poly lactide-co-glycolide (PLGA) nanoparticles (NPs) immobilized with anti-tuberculosis (anti-TB) drug — isoniazid (INH) by applying the Taguchi method and Design Expert statistical software. Several experiments were performed with varying parameters, namely polymer/drug ratio, polyvinyl alcohol (PVA) concentration, the ratio of organic solvent to the aqueous phase, and solvent type. Three different levels and a fractional factorial design were derived for each parameter, particularly the standard orthogonal array (OA) L<sub>9</sub>. Drug-loaded nanoparticles were prepared by the double emulsion method. The results were obtained from 9 runs indicated particle sizes ranging from 152.2±6.4 nm to 496.4±9.5 nm. These results were used to predict the optimum conditions for synthesizing INH-PLGA particles. The calculated data correlate well with the experimental data. INH-PLGA NPs were obtained with a mean size and polydispersity of nanoparticles of 152.2±2.25 nm and 0.279±0.03, respectively. Scanning electron microscopy, thermogravimetric analysis, and differential scanning calorimetry were carried out to characterize the obtained nanoparticles. The degree of drug release from PLGA NPs was studied, and the results showed that PLGA prolonged the release of INH from the polymer matrix.

**Keywords:** isoniazid, nanoparticles, Taguchi method, poly lactide-co-glycolide, double emulsion, anti-TB drug, experimental design, biopolymers.

### *Introduction*

Nanoparticles (NPs) based on polymers have drawn a major interest in biomedical research, in particular for drug delivery applications of anti-tuberculosis (anti-TB) drugs. Drug delivery based on polymeric NPs has shown perspective for addressing poor bioavailability, toxicity, and long-term treatment of tuberculosis or overcoming the side effects of anti-TB drugs. It has been successfully used in various preclinical studies [1]. Polymeric materials, namely polylactide, poly butyl cyanoacrylate, and poly lactide-co-glycolide (PLGA), have generated considerable interest in encapsulating various therapeutic agents [2–4]. Nanoparticles prepared from these and other polymers have been investigated and used as delivery systems for anti-TB drugs [5–7]. PLGA is one of the promising carriers. It is one of the few polymers that the Food and Drug Administration (FDA) has approved for use in humans due to its biocompatibility and biodegradability [8, 9]. In this study, we used PLGA as a carrier to prepare isoniazid (INH) loaded NPs.

There are different methods to produce PLGA-based nanoparticles: Simple emulsion, double emulsion, salting-out, nanoprecipitation, microfluidic technology, flow focusing, and membrane emulsification [8, 11]. All these methods for the production of PLGA NPs share a common feature of mixing a PLGA dispersed organic phase with a non-solvent. Evaporation, extraction, and/or combinations are commonly used for solvent removal [8, 10, 11].

Physicochemical properties of the obtained NPs, such as particle size, polydispersity, encapsulation efficiency (EE) and NPs' yield, play an important role. In addition, particle size is an important characteristic when passively targeting macrophages since it affects the success of internalization in these cells. In this respect, particles with a diameter of approximately 500 nm are ideal for phagocytosis by alveolar macrophages [7, 12]. Therefore, this work aims to develop and optimize the conditions for obtaining PLGA nanoparticles and immobilizing INH in them. A controlled INH delivery system with high drug loading and EE, as well as NPs' yield should be obtained. Polymeric nanoparticles containing INH were prepared using the double emulsion (W/O/W) method. The Taguchi design method was used to optimize the nanoparticle preparation method. The Taguchi design method is a fractional factorial design that uses an orthogonal array (OA), which can considerably reduce the number of experiments. The effects of the proposed experiments on the

responses were analyzed using Design Expert (test version 13, Stat-Ease, Minneapolis, USA) to independently obtain the main effects of these factors. Then an analysis of variance (ANOVA) was performed to determine the statistically significant factors [12–14]. In this way, various parameters such as ratio and type of organic solvent, surfactant concentration, and polymer/anti-TB drug ratio were investigated. A selection function determined the optimal conditions. The resulting formulation was characterized by analysis of variance (ANOVA), which can be used to estimate the influence of factors on the characteristic properties. In addition, we investigated the release kinetics of the INH drug *in vitro*.

### Experimental

Isoniazid (INH) with indicated purity over 99 %, polyvinyl alcohol (PVA) (hydrolyzed, MW 9000-10000) and polylactide-co-glycolide (PLGA 50:50, MW 24,000-38,000) were purchased from Sigma Aldrich (Germany). Ethyl acetate (EA) and dichloromethane (DCM), sodium phosphate dibasic and potassium phosphate monobasic were obtained from Component Reagent (Russia).

#### **Preparation of polylactide-co-glycolide nanoparticles immobilized with isoniazid.**

INH-loaded PLGA NPs were prepared by a double emulsion method [12]. 1 mL of an aqueous INH solution was first emulsified in 5 mL of solvent (EA, DCM, or mixture of EA/DCM 50/50) containing PLGA (INH/PLGA ratio: 1/1-1/5 by weight) for 2 min using a homogenizer (Ultra-Turrax T-10, IKA, Germany). The resulting primary emulsion was added to 0.5-2 % PVA (at an organic /aqueous phase ratio from 1/1 to 1/10); the mixture was then homogenized using a homogenizer for 3 min to form a secondary emulsion. The secondary emulsion was stirred continuously for 6 hours on a magnetic stirrer to completely remove solvent at room temperature. INH-loaded PLGA NPs were extracted by centrifugation (MiniSpi, Eppendorf, Hamburg, Germany) (14,000 rpm, 20 min). The resulting nanoparticle suspension was rinsed with distilled water using three centrifugation steps at 14,000 rpm for 15 min each to remove dissolved solids and organic solvent from the mixture.

#### **Determination of particle size, polydispersity (PDI)**

Particle size and PDI of nanoparticles were determined using photon correlation spectroscopy (PCS) on a Zetasizer Nano S90 from Malvern (Malvern Instruments Ltd., Malvern, UK). Samples were diluted in distilled water. Each dimensional analysis lasted 120 seconds and was carried out at 298 K with a 90° angle determination. Measurements were conducted in triplicate ( $n = 3$ ). The surface morphology of INH-PLGA NPs was analysed with a scanning electron microscope (SEM) (MIRA 3 LM TESCAN, Czech Republic).

#### **Encapsulation efficiency and yield of PLGA NPs**

The amount of isoniazid encapsulated in PLGA NPs was quantified by measuring the amount of unencapsulated isoniazid in the supernatant after centrifugation and particle washing. The amount of free INH was determined using a UV spectrophotometer at 262 nm. The EE and NPs yields were calculated as below:

$$\text{Encapsulation efficiency (EE\%)} = \frac{\text{Mass of the total drug} - \text{Mass of free drug}}{\text{Mass of total drug}} \times 100 \%;$$

$$\text{Nanoparticles yield (\%)} = \frac{\text{Mass of total nanoparticles}}{\text{Mass of the total drug} + \text{Mass of total PLGA}} \times 100 \%.$$

#### **In vitro study of drug release from PLGA NPs**

*In vitro* drug release experiments were carried out to determine the extent of INH release from PLGA NPs. NPs (24 mg) were re-dispersed in 14 mL of phosphate-buffered saline (PBS, pH 7.4) and kept at 335 K with stirring. Periodically, samples of the dialysates were taken (3 mL at a time). The amount of released drug was recorded on a UV-spectrophotometer (Promekolab, Russia) at wavelength  $\lambda_{\text{max}} = 262$  nm for the drug compared to the pure PBS.

#### **Thermogravimetric analysis and differential scanning calorimetry**

Thermogravimetric and differential thermal analysis were performed on a LabSYS evo TGA/DTA/DSC analyser (Setaram, France) in the temperature range of 30-550 °C in an aluminum oxide crucible at a heating rate of 10 °C/min in nitrogen inert medium and flow rate was 30 mL/min by decomposition of a nanoparticle sample.

## Results and Discussion

### Optimization of Nanoparticles Preparation

In our research work, the Taguchi method was used to optimize the immobilization of the biologically active substance isoniazid into PLGA nanoparticles. Four important factors influencing nanoparticle size and polydispersity (PDI) were as follows: Solvent type, INH/PLGA ratio, organic phase / aqueous phase volume ratio and PVA concentration. Three different levels and a fractional factorial design were derived for each parameter, particularly the standard OA L9 (Table 1).

Table 1

**Selected process parameters and corresponding levels in the Taguchi experimental design**

Process parameters	Level 1	Level 2	Level 3
Solvent type	DCM	EA/DCM	EA
INH/PLGA ratio	1/1	1/2.5	1/5
Organic solvent/water phase ratio	1/1	1/5	1/10
PVA concentration (%)	0.5	1	2

Taguchi's design was used to determine the significant factors that affect the size of INH-PLGA NPs. Considering four factors to be investigated, non-usage of an experimental design would have resulted in  $3^4 = 81$  separate experiments, which would have been difficult and inefficient. Instead, the Taguchi OA L9 design allowed nine experiments to determine the optimum conditions for each factor in achieving the smallest size of INH-PLGA NPs. By using these optimal results, PLGA nanoparticles immobilized with drug were synthesized. The results are shown in Table 2.

Table 2

**Structure of the Taguchi OA L9, corresponding particle size and polydispersity**

No.	Solvent type	INH/PLGA ratio	Organic solvent/water phase ratio	PVA concentration (%)	Size (nm)	PDI
1	EA	1/1	1/5	1	282.6±16.6	0.485±0.02
2	EA	1/2.5	1/1	0.5	160.2±32	0.101±0.05
3	EA	1/5	1/10	2	403.6±15.7	0.654±0.06
4	DCM	1/1	1/1	0.5	496.4±9.5	0.837±0.08
5	DCM	1/5	1/5	2	265.7±18.5	0.681±0.03
6	DCM/EA	1/1	1/5	0.5	365.8±4.4	0.8±0.03
7	DCM/EA	1/1	1/10	1	422.6±8.4	0.678±0.05
8	DCM/EA	1/2.5	1/1	1	189.6±18.4	0.518±0.02
9	DCM/EA	1/5	1/5	2	152.2±6.4	0.285±0.02

Table 2 shows the results for the diameters of PLGA nanoparticles obtained by PCS. It can be seen from the above numbers that PLGA nanoparticles have satisfactory physicochemical characteristics. The results obtained from 9 runs showed that the particle size ranged from 152.2±6.4 nm to 496.4±9.5 nm.

After these indicators, the experiments results were analyzed. Design-Expert software developed to independently obtain the main effects of these factors and then analysis of variance to determine the statistically significant factors was developed using ANOVA table [12–14]. The ANOVA tables for mean size and PDI are presented in Table 3. When the raw data were analyzed by ANOVA, the results showed that solvent type had no effect on mean particle size and PDI. Therefore, this parameter does not appear in the ANOVA analysis. For the mean particle size (Table 3a), the “P-value” for the model is below 0.05, indicating that the model is significant. The ratios of INH/PLGA and organic solvent/aqueous phase are significant conditions of the model, while the concentration of PVA can be considered as not significant. By removing the non-significant variable, the model can be improved. Although PVA concentration has a “P-value” of 0.4, this variable was still included in the model because the model becomes significant when this parameter is retained.

The PDI values were analyzed similarly to the mean particle size. In the ANOVA table (Table 3b), the “P-value” for the model is greater than 0.05, indicating that the model is not significant. The “F-value” of the model is 1.14, indicating that the model is not significant with respect to noise. The probability that such a

large “F-value” could arise due to noise is 48.83 %. In this case, the concentrations of INH/PLGA ratio, organic solvent/water phase ratio, and PVA concentration are all significant conditions to support the model structure since we did not consider the effect of noise (stirrer speed and sonication time) on the PDI values in the nanoparticle preparation process.

Table 3

ANOVA for selected factorial model

Source	Sum of Squares	Degrees of freedom	Mean Square	F-value	P-value	
(a) Size (nm)						
Model	97158.79	5	19431.76	17.28	0.0203	Significant
B — INH/PLGA ratio	59358.26	2	29679.13	26.39	0.0125	
C — Organic solvent/water phase ratio	31538.13	2	15769.07	14.02	0.0300	
D — PVA concentration (%)	1032.32	1	1032.32	0.9178	0.4087	
Residual	3374.50	3	1124.83			
Cor Total	1.005E+05	8				
(b) PDI						
Model	0.2533	5	0.0507	1.14	0.4883	Not significant
B — INH/PLGA ratio	0.1851	2	0.0925	2.08	0.2712	
C — Organic solvent/water phase ratio	0.0257	2	0.0129	0.2889	0.7678	
D — PVA concentration (%)	0.0029	1	0.0029	0.0643	0.8162	
Residual	0.1335	3	0.0445			
Cor Total	0.3868	8				

Figure 1 shows the different effect of the independent variables on the average nanoparticle size and PDI. The smallest size and PDI of nanoparticles are observed with INH/PLGA ratios of 1/2.5 and organic solvent/water phase of 1/5. With increasing PVA concentration, the particle size decreases and the PDI increases.

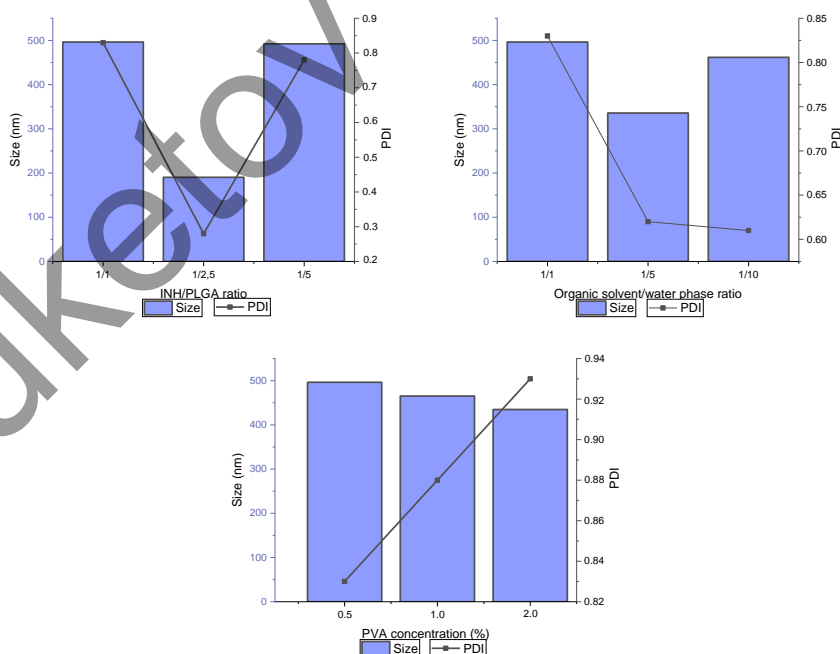


Figure 1. Influence of parameters on particle size and polydispersity

After processing the data by ANOVA, parameters were selected to optimize the process to obtain particles with minimum size and PDI (Table 4).

Table 4

**Optimum solutions for synthesis of INH-PLGA NPs**

Name	Goal	Lower Limit	Upper Limit	Lower Weight	Upper Weight	Importance
A — Solvent type	is in range	DCM	EA	1	1	3
B — INH/PLGA ratio	is in range	1/1	1/5	1	1	3
C — Organic solvent/water phase ratio	is equal to 1/5	1/1	1/10	1	1	3
D — PVA concentration (%)	is in range	0.5	2	1	1	3
Size	Minimize	152.2	496.4	1	1	3
PDI	Minimize	0.101	0.83	1	1	3

The best parameters for obtaining INH-PLGA NPs were as follows: solvent type — DCM and EA mixture, INH/PLGA ratio 1/5, PVA concentration 1 %, and organic solvent to aqueous phase ratio 1/5. Under these conditions, the software estimated a nanoparticle size of 150.65 nm, while the nanoparticle size obtained from the experiment was  $152.2 \pm 2.25$  nm, as shown in Figure 2. Experiments were carried out to confirm the optimum parameters obtained by the Taguchi method. A good agreement was observed between the predicted particle size and the experimental particle size (Table 5). Consequently, the size of the synthesized isoniazid-loaded polylactide-co-glycolide nanoparticles can be improved using the Taguchi method.

Table 5

**Predicted and experimental results for INH-PLGA NPs**

	Size (nm)	PDI
Predicted	150.65	0.232
Experimental	$152.2 \pm 2.25$	$0.279 \pm 0.03$
Error %	1.03	20.3

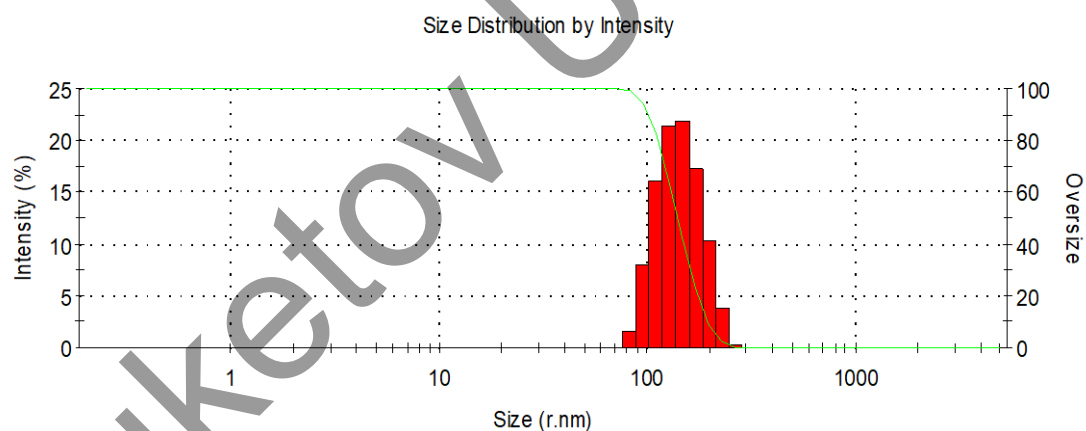


Figure 2. Histogram of particle size distribution of INH-PLGA NPs obtained under optimum conditions

**Physicochemical characteristics of PLGA NPs immobilized with isoniazid**

Morphological analysis of the polymeric nanoparticles was performed using a scanning electron microscope (SEM) MIRA 3 LM TESCAN (Czech Republic). The obtained images are shown in Figure 3. Micrographs of nanoparticle samples show both single particles and their agglomerates. The systems mainly consist of particles of the same size in the range of 100–250 nm, but larger particles (over 300 nm) are also present. We suggest that they are formed in combining nanoparticles by evaporation of the organic solvent.



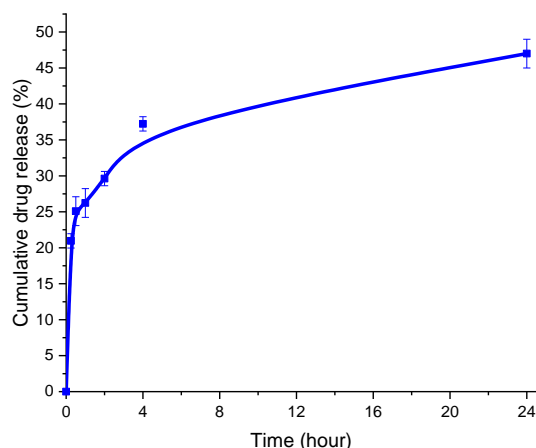


Figure 5. Release rate of isoniazid from polylactide-co-glycolide nanoparticles

### Conclusions

This study has shown that the size of polylactide-co-glycolide nanoparticles with isoniazid synthesized by the double emulsion method can be controlled by changing the process conditions. The smallest size and PDI of nanoparticles are observed with INH/PLGA ratios of 1/2.5 and an organic solvent/water phase of 1/5. The particle size decreases with increasing PVA concentration, and the PDI increases. Using the Taguchi method, it has been found that the INH/PLGA ratio has the most significant effect on the size of polylactide-co-glycolide nanoparticles. The Taguchi method is one of the most suitable methods for optimizing the experimental conditions to achieve the minimum PLGA nanoparticle size for drug delivery systems. The obtained nanoparticles have been characterized by PCS, which shows that the system consists of rather small particles of  $152.2 \pm 2.25$  nm. The obtained particles have a narrow particle size distribution (PDI =  $0.279 \pm 0.03$ ). The drug loading and encapsulation efficiency are 67 and 83 %, respectively. The yield of INH-PLGA NPs is 45 %. The synthesized NPs have a spherical morphology and average size of less than 300 nm. The results of in vitro study show that PLGA prolongs the release of INH from the polymer matrix. The obtained INH-PLGA NPs have satisfactory physicochemical parameters for further application as targeted drug transport systems.

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### **Изониазидпен иммобилизацияланған полилактид-со-гликолид нанобөлшектері: Тагучи эксперименттік әдісінің көмегімен оңтайландыру**

Зерттеудің мақсаты изониазидпен (INH) иммобилизацияланған полилактид-со-гликолидін (PLGA) нанобөлшектерін (НБ) алу үшін Тагучи әдісі мен Design Expert статистикалық бағдарламаны қолдану арқылы оңтайландыру және эксперименттер санын азайту болып табылады. Полимер мен дәрілік заттың қатынасы, поливинил спиртінің (ПВС) концентрациясы, органикалық еріткіш пен су фазасының қатынасы және еріткіштің түрі сияқты параметрлерді түрлендіру кезінде бірқатар эксперименттер жүргізілді. Әрбір параметр үшін үш түрлі деңгей және бөлшек факторлық конструкция, атап айтқанда, стандартты ортогональды матрица L9 алынды. Дәрілік препаратпен жүктелген нанобөлшектер қос эмульсия әдісімен алынды. 9 эксперимент барысында алынған нәтижелерге сүйене отырып, бөлшектердің көлемі 152,2±6,4 нм-нен 496,4±9,5 нм-ге дейін болғаны анықталды. Бұл нәтижелер PLGA– INH бөлшектері синтезінің оңтайлы жағдайларын болжау үшін пайдаланылды. Есептелген деректер эксперименттік мәліметтермен сәйкес келеді. PLGA — INH НБ-нің орташа мөлшері мен полидисперстілігі тиісінше 152,2±2,25 нм және 0,279±0,03 алынды. Алынған нанобөлшектерді сипаттау үшін мына физика-химиялық талдаулар жүргізілді: сканерлеуші электрондық микроскопия, термогравиметрлік талдау, дифференциалды сканерлеуші калориметрия. PLGA нанобөлшектерінен дәрілік заттың босап шығу дәрежесі зерттелді және алынған нәтижелер PLGA полимерлік матрицадан INH босату мерзімін ұзартатыны анықталды.

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### **Наночастицы полилактид со-гликолида, иммобилизованные изониазидом: оптимизация с помощью экспериментального метода Тагучи**

Целью настоящего исследования была оптимизация и минимизация количества экспериментов для получения наночастиц (НЧ) полилактид со-гликолида (PLGA), иммобилизованных изониазидом

(INH), путем применения метода Тагучи и статистического программного обеспечения Design Expert. Проведен ряд экспериментов при варьировании параметров: соотношение полимера и лекарственного препарата, концентрация поливинилового спирта, соотношение органического растворителя и водной фазы и тип растворителя. Для каждого параметра были получены три различных уровня и дробная факторная конструкция, в частности, стандартная ортогональная матрица L9. Наночастицы, загруженные лекарственным препаратом, были получены методом двойной эмульсии. Результаты, полученные в ходе 9-ти экспериментов, показали, что размер частиц варьировался от  $152,2 \pm 6,4$  до  $496,4 \pm 9,5$  нм. Полученные данные были использованы для прогнозирования оптимальных условий синтеза частиц PLGA–INH. Рассчитанные результаты хорошо коррелируют с экспериментальными. Получены НЧ PLGA–INH со средним размером и полидисперсностью наночастиц  $152,2 \pm 2,25$  нм и  $0,279 \pm 0,03$ , соответственно. Для характеристики полученных наночастиц были проведены следующие физико-химические анализы: сканирующая электронная микроскопия, термогравиметрический анализ, дифференциальная сканирующая калориметрия. Была изучена степень высвобождения лекарства из НЧ PLGA, и результаты показали, что PLGA пролонгирует высвобождение INH из полимерной матрицы.

*Ключевые слова:* изониазид, наночастицы, метод Тагучи, полилактид со-гликолид, двойная эмульсия, противотуберкулезный препарат, экспериментальный дизайн, биополимеры.

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