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Research Article

Impact of ultrasound and medium condition on production of selenium-enriched yeast ☆

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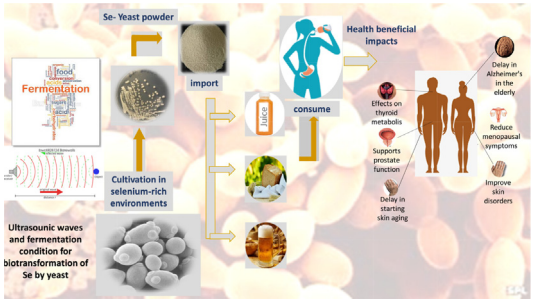
GRAPHICAL ABSTRACT



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ABSTRACT

Background: Ultrasonication was used to stimulate the growth and selenium (Se) biotransformation in *Saccharomyces cerevisiae*. An optimization study for maximal Se accumulation in *S. cerevisiae* was conducted using the Plackett–Burman screening method and response surface methodology (RSM) for optimization of conditions. The variables influencing Se biotransformation by yeast, including duration and power of ultrasound, inoculum treatment with ultrasound, duty cycle, growth phase, time, shaking rate, inorganic salt concentration (Se, Zn, Mg, and K), and nitrogen and carbon sources as well as their concentrations were screened using the Plackett–Burman design.
Results: The main variables were carbon and Se concentration as well as ultrasound power and duty cycle. The lack of fit was insignificant ($P > 0.01$). The optimum condition for Se accumulation was obtained at Se concentration of 60 μg/ml, carbon source brix of 15, ultrasound of 90 W/L, and duty cycle of 40%.
Conclusions: The results showed that optimization of parameters and application of ultrasonication lead to a successful enhancement (2.78-fold) in the accumulation of selenium by *S. cerevisiae.* Such enriched yeast can be utilized in bread for increasing consumption of Se in the diet of patients with Se deficiency.
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1. Introduction

Selenium (Se) plays a critical role in the function of selenoproteins and several antioxidant selenoenzymes in human body. This metal protects against cancer, cardiovascular diseases, infertility, and diabetes [1,2,3] It also stimulates the immune system function and leads to an increase in antibody synthesis (IgG and IgM) [4,5]. Organic Se compounds have higher absorption and lower toxicity than inorganic Se species. Few plants can accumulate Se from soil [3], while *Saccharomyces cerevisiae* can biotransform inorganic Se into an organic form. Se-enriched yeast (SeY) is an economic source of organic Se for fortification of fermented foods with SeY, especially in bread as a dominant food from children to adults in many countries [6]. Such SeY can be used for human consumption and for individuals with Se deficiency [7].

Novel nonthermal technology such as pulsed electric fields (PEF) and sonication possesses enormous applications in fermentation processes because of increasing cell permeability [8,9] and porosity in the cell membrane [10]. Thus, these novel methods are appropriate approaches for the enrichment of elements in yeast. Ultrasonication has been reported to significantly increase Ca^{2+} concentration in yeast [11].

Few studies have reported the influence of culture conditions on the production of SeY, including concentration and source of inorganic Se, pH, time, temperature, aeration, agitation, seed age, glucose condition, and size, on the yield of incorporated Se, (μg incorporated Se/g yeast) and growth (g produced biomass/l medium) [6]. Optimization of the process variables that influence Se biotransformation enhances Se load and yeast growth [12]. Few studies have reported the impact of pulsed electric fields (PEF) on the accumulation of metal ions in *S. cerevisiae* [13]. After screening design, the main and interaction impact of variables and fitting the best models was evaluated by a response surface methodology (RSM) like Box-Behnken [6,12]. In a review, all process variables influencing SeY production has been summarized elsewhere [2].

None of the studies have focused on the simultaneous impact of process variables and ultrasound on stimulating Se biotransformation in yeast. To the best of our knowledge, the present study is the first report on the application of ultrasonic waves to Se biotransformation in *S. cerevisiae*. A total of 15 factors were screened by Plackett-Burman design (PBD). Next, for further optimization step, Box-Behnken design (BBD) was used to evaluate the main and interaction impact of the main variables include brix (or carbon concentration), initial Se concentration, ultrasound power, and duty cycle on Se biotransformation and growth.

2. Materials and methods

Sodium selenite used for the enrichment of *S. cerevisiae* was purchased from Sigma Chemical Company. All chemicals for the enrichment of culture were of analytical grade and purchased from Merck Company.

2.1. Microorganism and inoculum preparation

S. cerevisiae (ATCC 9763) was obtained from microbial collection of Alzahra University, Tehran, Iran. It was then grown on Sabouraud's Dextrose Agar (SDA) for 48 h at 30°C. The pre-inoculum was inoculated with one or two loop-full of colonies from 100 mL of sterile medium containing peptone 5.0 g/L, yeast extract 3.0 g/L, glucose 10.0 g/L and incubated at 30°C for 24 h at the shaking rate of 180 rpm [2,14].

Table 1
Plackett Burman Design for the evaluation of 15 process variables on Se-enriched yeast.

No	Carbon source	Brix of carbon source	Nitrogen source	Nitrogen concentration (g/l)	Se concentration (μg/ml)	Zn concentration (μg/ml)	Mg concentration (g/l)	K concentration (g/l)	Time of incubation (h)	Shaking (rpm)	Ultrasound duration (h)	Growth phase for treatment	Power of ultrasound (watt)	Inoculum treated with ultrasound	Duty cycle (%)	Dried Cell Weight (g/L)	Organic Se (mg/L)	
																	Predicted	Observed
1	1	20	0	7.5	40	100	0.3	2.5	48	130	2.5	0	140	1	60	10.8	164.8	164.8
2	1	45	0	7.5	15	1000	0.3	0	48	180	0.5	1	70	1	60	1.4	23.7	0.0
3	1	45	1	7.5	15	100	2	0	24	180	2.5	0	140	0	60	0.6	0.0	0.0
4	1	45	1	15	15	100	0.3	2.5	24	130	2.5	1	70	1	20	0.5	0.0	0.0
5	0	45	1	15	40	100	0.3	0	48	130	0.5	1	140	0	60	9.8	91.4	91.4
6	1	20	1	15	40	1000	0.3	0	24	180	0.5	0	140	1	20	11.9	136.3	139.4
7	0	45	0	15	40	1000	2	0	24	130	2.5	0	70	1	60	7.6	182.8	182.8
8	1	20	1	7.5	40	1000	2	2.5	24	130	0.5	1	70	0	60	9.2	210.8	210.8
9	1	45	0	15	15	1000	2	2.5	48	130	0.5	0	140	0	20	0.6	0.0	0.0
10	0	45	1	7.5	40	100	2	2.5	48	180	0.5	0	70	1	20	8.6	30.5	123.2
11	0	20	1	15	15	1000	0.3	2.5	48	180	2.5	0	70	0	60	11.4	42.8	42.8
12	1	20	0	15	40	100	2	0	48	180	2.5	1	70	0	20	10.1	154.8	154.8
13	0	45	0	7.5	40	1000	0.3	2.5	24	180	2.5	1	140	0	20	10.2	125.2	125.2
14	0	20	1	7.5	15	1000	2	0	48	130	2.5	1	140	1	20	12.3	32.4	35.5
15	0	20	0	15	15	100	2	2.5	24	180	0.5	1	140	1	60	6.2	25.9	25.9
16	0	20	0	7.5	15	100	0.3	0	24	130	0.5	0	70	0	20	11.2	21.6	21.6

2.2. Fermentation medium preparation

The preparation of fermentation medium for *S. cerevisiae* was performed by the method of Esmaeili et al. [2] with some modifications. The medium contained $ZnCl_2$ (100 and 1000 µg/ml), $MgCl_2{\cdot}6H_2O$ (0.3 and 2 g/L), thiamine 0.2 g/L; calcium pantothenate 0.025 g/L; sodium citrate 15 g/L, and KH_2PO_4 (0 and 2.5 g/L) [13,15,16,17]. Either sugar beet molasses or date wastes in different brix (20 and 45%) were added as economical agro-industrial by-product carbon sources [13]. Chemical characteristics of the carbon sources were analyzed according to the standard methods. The results for molasses and date waste were as follows: degree of brix, 78.5 and 87.5; total sugar 32.67% and 66.19%; ash 2.14% and 10.38%, respectively. For nitrogen source screening either NH_4Cl or yeast extract was used in different concentrations (7.5 and 15 g/L). The initial Se concentrations in the medium were 15 and 40 µg/ml [2,14]. The pH of the fermentation medium was adjusted at 5.5 with HCl and NaOH after autoclaving (121°C, 20 min, ReyhanTeb, Iran) [6], the seed culture was inoculated at 10% (v/v) into 90 ml of fermentation medium, and incubation was performed at 30°C and (130 and 180) rpm for 24 and/or 48 h [2].

2.3. Determination of cell biomass yield of yeast

Cell biomass yield of Se-enriched yeast was determined by centrifugation. Briefly, 10 ml yeast culture (4500 × *g*, 10 min, 4°C) was centrifuged, and the supernatant was discarded. Pellet including yeast cells were dried at 80°C to constant weight [14].

As a criterion of the yeast growth in the media containing molasses or date waste, the optical density (OD) was measured by a spectrophotometer (Spectronic 70 Bausch & Lomb) at the wavelength of 540 nm. After centrifugation of fermentation culture (5000 rpm, radius 15 cm for 5 min), the pellet was resuspended in pure water, and OD was measured using a spectrophotometer (PerkinElmer, USA) at 600 nm [14].

2.4. Determination of Se content in yeast

After centrifugation (3500 × *g* for 5 min), yeast cells were rinsed three times with deionized water to remove adsorbed Se. During drying under vacuum, the weight of pellets was measured until reaching a constant weight. Se determination was performed based on the inductively coupled plasma optical emission spectroscopy (ICP-OES) (VISTA-PRO, USA) method. Briefly, 100 mg dried yeast was digested (20 min for 105°C) with 3 ml of concentrated HNO_3. HCl was then added and heated (10 min for 80°C) for completing the digestion and measurement of total Se. To measure inorganic Se, the dried cell suspended in ultra-pure water and inserted in a boiling bath for 1 h. After centrifugation (15 min at 8300 × *g*), inorganic Se was measured in the supernatant [2].

2.5. Plackett–Burman design

PBD was used to find the main variables influencing Se bioaccumulation among the 15 process variables include duration of ultrasound, power of ultrasound, inoculum treatment with ultrasound, duty cycle, growth phase (either lag or log), incubation time, shaking rate, different types of carbon sources (molasses and date waste), the initial concentrations of carbon source, inorganic salts concentration (Se, Zn, Mg, and K), nitrogen sources (ammonium chloride and yeast extract), and their concentrations. The design comprised 16 runs at low (−) or high (+) levels. The upper and lower level for each parameter were selected based on the preliminary studies [1,2]. Significant parameters were selected according to the content of organic Se taken as the response. Assuming that there was no interaction among the variables, a first-order polynomial model was exerted for fitting PBD as **Equation 1**:

$$Y = \beta 0 + \sum_{i=1}^{16} \beta i Xi \qquad \text{Equation1}$$

where Y is the predicted response; β0 is the intercept; βi is the linear regression coefficient, and Xi is the coded independent variable [2].

2.6. Box–Behnken design

The influence of four effective independent variables on organic Se content was determined by BBD, including the degree of brix, Se concentration, ultrasound power, and duty cycle. Each variable level was obtained from pretests according to PBD. In the following, the best conditions for Se biotransformation were determined by the Box-Behnken design [6,12]. To optimize Se bioaccumulation, a three-level BBD 29 runs in 5 replicates of center point were performed. Content of organic Se was considered as the response. **Equation 2** demonstrates the RSM model as a quadratic polynomial equation

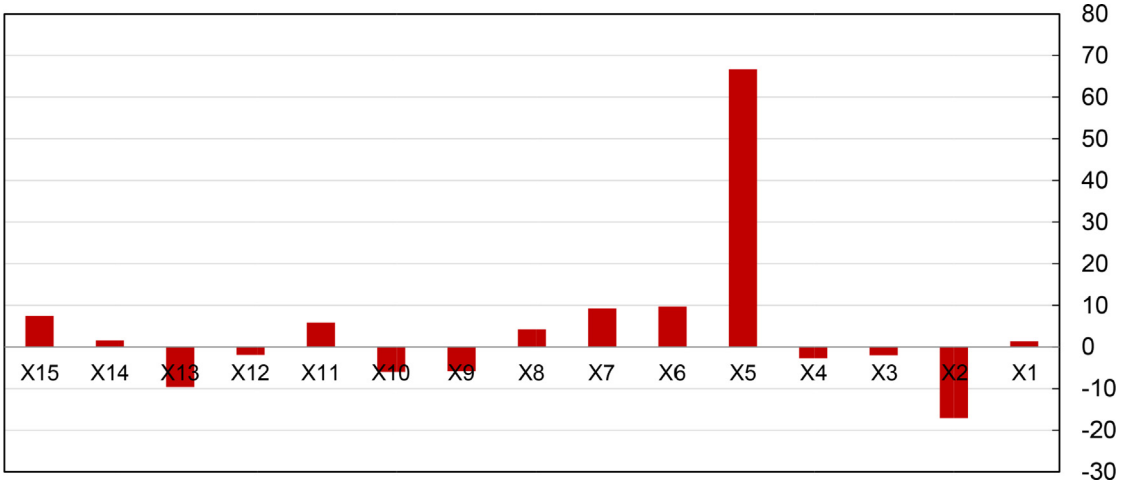

Fig. 1. Coefficient of process variables in Plackett-Burman design for the production of Se-enriched yeast.

[2]:

$$Y = \beta 0 + \sum_{i=1}^{4} \beta iXi + \sum_{i=1}^{4} \beta iiXi^2 + \sum_{i=1}^{3} \sum_{j=i+1}^{4} \beta ijXiXj \qquad \text{Equation2}$$

where Y is the predicted response; β0, βi, βii and βij are regression coefficients of the intercept, linear, quadratic, and interaction terms, respectively; and Xi and Xj are coded independent variables.

2.7. Ultrasonic treatment

The ultrasonic apparatus (the Top Sonics group, Iran) included a titanium probe operating at a fixed frequency of 20 kHz (maximum power: 400 W). A cooling bath was used to prevent overheating and control temperature. To avoid cross-contamination, ultrasonication was performed in a cabinet (ambient temperature). Before fermentation, the pre-inoculum was sonicated (20 kHz, 140 W/l,

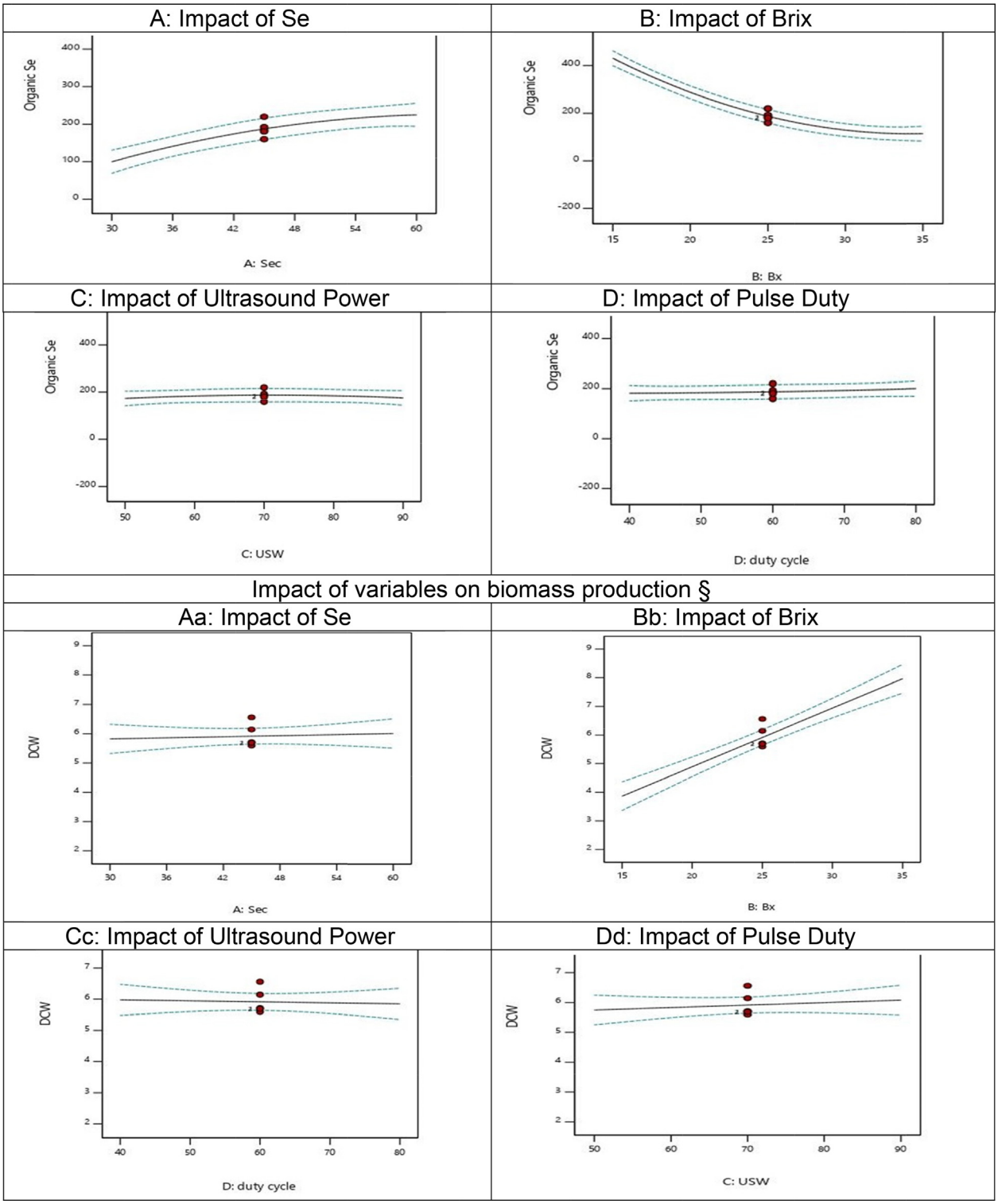

Fig. 2. Contour plots of main effects of organic Se concentration (A), Brix (B), ultrasound power (C), and pulse duty (D) on growth (§) and Se (*) transformation in *S. cerevisiae*.

1 s ON and 10 s OFF) [15]. Ultrasonic irradiation was applied at two different power values (70 or 140 W/l), duty cycle (20 or 60%), and growth phase (lag or logarithmic phase), durations (0.5 or 2.5 h) at 30°C in 250 ml Erlenmeyer containing 100 ml fermentation medium [18].

2.8. Statistical analysis

Statistical analysis was performed by MINITAB statistical software (Version 16), and response surface plots were drawn. Data were treated statistically with analysis of variance (ANOVA) and presented as mean value ± SD (standard deviation) on various days. $P \leq 0.05$ was considered statistically significant. Comparison between the treatment groups were carried out using one way analysis of variance (ANOVA), SPSS Software v.23.0 and Tukey HSD with a statistically significance level of P-value ≤ 0.05. Results were regenerated three times and expressed as means ± SD (standard deviation).

3. Results

3.1. Growth curve of S. cerevisiae

The growth curve of *S. cerevisiae* was plotted to identify different growth phases. The latent phase for date waste and molasses as the carbon source was completed within 6.5 h and 9.5 h, respectively, and the logarithmic phase for both of them was completed in 23 h.

3.2. Analysis of PBD experiments

Fifteen variables were analyzed to evaluate their impact on the accumulation of Se using a PBD (Table 1). To find cost-effective fermentation conditions for SeY production by *S. cerevisiae*, four significant variables were selected by PBD and optimized using BBD. The variables coefficient is exhibited in Fig. 1. After screening 15 dependent variables in SeY production, 4 effective factors with higher impact coefficient, including the degree of brix, Se concentration, ultrasound power, and duty cycle, were selected to optimize effective process variables by Box Behnken design.

4. Discussion

Fig. 1 shows that the degree of high level of brix and ultrasound power had negative impact on response, whereas the other variables (Se, Zn, Mg concentration, and duty cycle) increase the bioaccumulation process at their high level. As shown in Fig. 1, few variables showed the most important contribution, and the importance of all variables was not the same. According to the results (Fig. 1 and Fig. 2), Se concentration, with a coefficient of 66.66, was the most effective factor for Se biotransformation, followed by the degree of brix (17.06), Zn concentration (9.67), ultrasound power (9.62), magnesium concentration (9.24), and duty cycle (7.42).

The selection of variables for further experiment was performed based on statistics and nonstatistical observations. As the main purpose of this research has been focused on Se biotransformation, 4 main variables with the greatest impact were selected as carbon and Se concentration as well as ultrasound power and duty cycle.

A high coefficient (absolute value) shows a more effective impact on the response. The results demonstrated Se, Zn, and Mg concentration had direct effects on the bioaccumulation process, which was similar to that observed in previous studies. Previous reports showed regression between the concentration of metals in media and rate of biotransformation, e.g. an increase in Se concentration [2,13,14] in the presence of Zn [13], and Mg [15], can lead to a rise in Se accumulation. Moreover, the content of organic Se enhanced with increasing Se concentration at low brix of carbon source (Fig. 3).

However, by increasing the concentration of Se in medium, the content of biotransformed Se increases especially in low Brix. This observation is probably due to *S. cerevisiae* JEN1 repression at high sugar concentrations [16]. McDermott indicates that Jen1p is a transporter that facilitates selenite accumulation inside the cells [17].

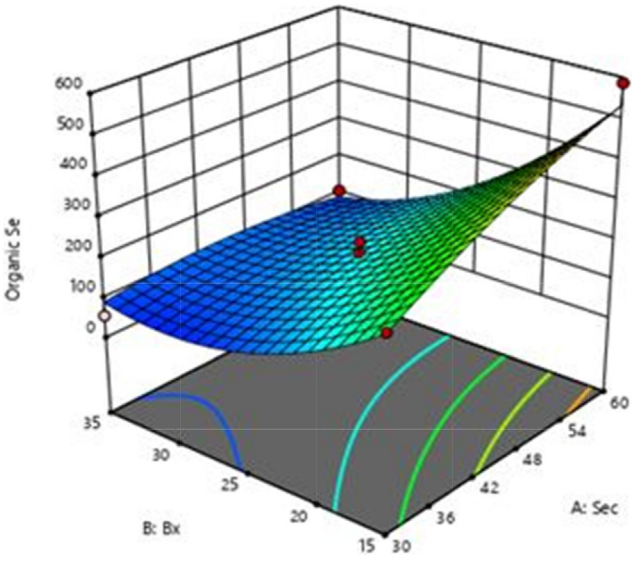

Fig. 3. Interaction effects between Se concentration and brix of carbon source on organic selenium content in *S. cerevisiae.*

Table 2
Box–Behnken design experiment for the optimization of process variable on growth and Se biotransformation of yeast.

No	Se µg/ml	Brix	Power watt	Duty cycle %	Dried Cell weight g/l	Organic Se mg/l
1	45	25	70	60	5.71	192.37
2	45	35	70	40	7.29	114.59
3	30	15	70	60	2.97	281.46
4	30	25	50	60	6.43	102.02
5	45	25	90	40	6.37	187.77
6	45	15	90	60	5.20	430.79
7	30	25	70	40	6.54	94.72
8	45	25	50	80	6.60	211.90
9	45	25	70	60	6.56	219.96
10	30	25	70	80	6.86	95.32
11	60	35	70	60	8.96	104.17
12	60	25	90	60	6.98	163.85
13	45	15	50	60	3.63	364.12
14	45	25	90	80	5.63	189.56
15	45	25	70	60	5.59	184.60
16	45	25	70	60	5.69	180.56
17	30	25	90	60	5.89	119.63
18	30	35	70	60	7.06	55.86
19	60	25	70	80	5.78	223.15
20	45	35	50	60	7.22	99.32
21	45	25	50	40	5.78	160.83
22	60	15	70	60	2.88	586.76
23	45	15	70	40	3.64	433.48
24	60	25	50	60	6.04	228.90
25	45	15	70	80	2.69	419.49
26	45	35	70	80	7.48	153.87
27	60	25	70	40	6.20	194.65
28	45	35	90	60	7.62	87.54
29	45	25	70	60	6.14	159.97

F-value of the model, and variables, including Se content, Brix, ultrasound power, and duty cycle, were 35.20, 53.78, 343.14, 0.0138, and 0.3136, respectively.

4.1. Analysis of Box Behnken experiments

For the optimization process, a 29-treatment combination was designed by the BBD method to analyze the 4 mentioned variables at 3 levels. The experimental data obtained from the 29 run given in Table 2 were analyzed using Design-Expert 11.0. Coefficient of determination (R^2 value) that shows the fitness of the model obtained from ANOVA. R^2 value for the content of organic Se was 0.9448, and a nonsignificant p-value for lack of fit (P = 0.2330) for the content of organic Se showed that the model was adequate to explain the experimental data. These results signified the quadratic polynomial model could elucidate 94.48% of the organic Se content results.

The results showed that the developed model used to fit the variables and response values were significant ($P \leq 0.01$) and fit to illustrate their correlations. The organic Se content results are shown in Table 2. The linear (A and B) and quadratic variables (A^2 and B^2) and interactive term (AB) (P-value < 0.05) were significant for the content of organic Se in yeast, while the interaction variables of AC, AD, BC, BD, and CD were insignificant. Fig. 2 can illustrate the impact of the chosen variables on Se accumulation. 3D contour plot can illustrate the interaction between Se concentration and brix of carbon source in Fig. 3.

Se accumulation also occurred in high sugar concentration (brix 35). This observation showed that ultrasound can improve the penetration of Se from medium through porous in the cellular membrane formed by sonication [18,19,20,21,22,23,24,25]. The maximum content of organic Se that was achieved in the screening step was 210.8 mg/L, while it was 586/765 mg/L in BBD. This finding showed that a successful enhancement (2.78-fold) in the accumulation of Se by *S. cerevisiae* was performed using a response surface methodology. Moreover, several studies demonstrated using agro-industrial byproduct such as molasses, corn bran, or soybean bran acid hydrolysates are effective substrates for carbon and nitrogen sources in the production of SeY, which is consistent with our results [19,20].

5. Conclusions

In the present study, the effect of ultrasonication was applied to stimulate biotransformation of Se by yeast. The optimum medium composition for Se accumulation was as follows: carbon source brix, 15; ultrasonic irradiation power, 90 W/L; Se concentration, 60 μg/ml; and duty cycle 40%. In the optimized condition, the accumulation of Se by *S. cerevisiae* was increased by 2.78-fold. Because ultrasonic induced cavitation alters the cell penetration, the effect of ultrasound on improving Se yeast biotransformation was studied in the present research. Based on high efficiency of Se biotransformation due to ultrasonic simulation, a partial replacement of SeY for production of bread is enough to reach a daily uptake of Se at the recommendation level. As daily consumption of bread in Iran is 150 g for adult in each serving, from total 2% w/w of yeast in sourdough, only 0.5% replacement by SeY can be applied for increasing consumption of Se in patients with Se deficiency. For future research, the investigation on the stability of complex of Se-metal in the shelf life of the product and gastrointestinal tract should be considered in simulated gastrointestinal condition and in vivo condition; otherwise, it could be lead to a sudden release in a limited place and time.

Author contribution

- Study conception and design: S Alijan, K Khosravi-Darani
- Data collection: S Alijan
- Analysis and interpretation of results: S Alijan, M Hosseini, S Esmaeili, K Khosravi-Darani
- Draft manuscript preparation: S Alijan, K Khosravi-Darani, M Hosseini, S Esmaeili
- Revision of the results and approved the final version of the manuscript: S Alijan, K Khosravi-Darani, M Hosseini, S Esmaeili

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Conflict of interest

The authors declared that there is no conflict of interest.

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