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OPTIMIZATION OF CoQ_{10} PRODUCTION BY A MUTANT OF *Cereibacter sphaeroides* GSPCDUBSR USING RESPONSE SURFACE METHODOLOGY

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ABSTRACT

While screening for a few novel bacterial strains capable of producing coenzyme Q_{10} (CoQ_{10}), a wild type *Cereibacter sphaeroides* strain GSPCDUBSR was isolated and identified. To increase the production of CoQ_{10} by this wild type strain, optimization of upstream process was carried out through response surface methodology (RSM). To maximize CoQ_{10} synthesis, a central composite design (CCD) was used to optimize the media composition which included sucrose, ammonium sulphate, peptone, and $MgSO_4$. The desire function approach was used to determine the ideal level for each element, and CoQ_{10} concentration were tracked as response variables. The results indicated that using the optimal culture composition (30 g L^{-1} sucrose, 15g L^{-1} ammonium sulphate, 25 g L^{-1} peptone, and 0.50 g L^{-1} $MgSO_4$) produced an average of 8.5 mg g^{-1} dry cell weight (DCW) of CoQ_{10}. Regression analysis results showed that the most efficient factors in generating CoQ_{10} were $MgSO_4$ and ammonium sulphate concentrations.

Keywords: *Cereibacter sphaeroides*, CoQ_{10} enzyme production, media optimization, RSM

INTRODUCTION

Coenzyme Q_{10} (CoQ_{10}), also known as ubiquinone-10, is a lipid-soluble quinone (CoQ) that is widely dispersed throughout organisms and functions as an electron carrier in the electron transport chain of aerobic respiration (Kawamukai, 2002). It also functions as an antioxidant by preventing oxidative damage to mitochondrial proteins and DNA, and protects lipids from peroxidation (Ernster and Dallner, 1995). This characteristic makes it a promising anti-aging agent for the cosmetics industry (Arkan Yousif *et al.*, 2025). According to medical research, the people suffering from diabetes, heart failure, and neurological disorders like Alzheimer's may benefit from taking CoQ_{10} supplements (Sood *et al.*, 2024).

The aromatic 2,3-dimethoxy-5-methyl-benzoquinone with a side chain of ten isoprenoid units make up coenzyme Q_{10}. The two precursors, decaprenyl diphosphate (DPP) and para-hydroxy-benzoate (pHBA) are used in its spontaneous synthesis. The CoQ species in *E. coli* are determined by the length of polyprenyl diphosphate (Asai *et al.*, 1994). Octaprenyltransferase UbiA mediates the condensation of octaprenyl diphosphate at pHBA's C3 position, and coenzyme Q8 (CoQ_8) is produced by a number of other changes at the aromatic ring (Young *et al.*, 1972). Simply expressing ddsA from

P. denitrificans, which codes for decaprenyl diphosphate synthase, allowed *E. coli* to produce CoQ_{10} by providing the precursor DPP (Takahashi *et al.*, 2003). This is because UbiA promiscuously recognizes isoprenoid diphosphates of various lengths (Suzuki *et al.*, 1994; Cheng and Li, 2014).

The anticipated yield of experimental run is produced by using the response surface method (RSM), which determines the correlation between process factors and response values. Applications of central composite design (CCD), a very successful experimental design methodology, can be found in many different fields of study (Cluis *et al.*, 2007; Kien *et al.*, 2010; Prout *et al.*, 2025). By successfully lowering the number of experimental tests, this technique lowers the expenses and chemical reagents needed. Even though a high-precision model might not be achievable, the methodical approach followed in this work is crucial to optimize CoQ_{10} production. In a previous study, a mutant of *C. sphaeroides* was successfully developed which help in increasing CoQ_{10} output (Kien *et al.*, 2010). In present paper we report the media component optimization for maximum CoQ_{10} production using a mutant strain *C. sphaeroides* GSPCDUBSR.

MATERIALS AND METHODS

Microorganism and fermentation experiments

For the isolation of wild type strain, soil samples were randomly collected from a sub-urban forest near Hyderabad, Telangana, India. Then 1 g composite sample was added to 10 mL saline, and thoroughly mixed for 30 min. It was then serially diluted ten folds before plating onto Luria Bertani agar medium and incubated for 48 h at room temperature. Pure culture obtained after repeated streaking on the same media was used for biochemical characterization and identification, which was tentatively identified as *Cereibacter sphaeroides*.

This strain *C. sphaeroides* was further used to develop potential high CoQ_{10} producing mutant. *C. sphaeroides* strain GSPCDUBSR was first grown on nutrient agar with ampicillin (20 µg mL^{-1}) gradient plate (to which *C. sphaeroides* strain was sensitive). Exposure of *C. sphaeroides* strain to this specific antibiotic and UV light for 20 min, produced around 10-15 mutants. Randomly these mutants were subjected to sodium azide gradient plate (20 mg 50 mL^{-1} nutrient medium). These mutants were found resistant to EMS with incubation time of 5 min. Then, these ampicillin, UV, sodium azide and EMS resistant mutants were subjected to a combination of high temperature (50ºC) with different incubation periods and Atorvastatin as the selection marker to test their viability and efficiency to produce CoQ_{10} in large scale. *C. sphaeroides* wild type strain after exposure at 50ºC showed 90% kill with 20 min incubation period, which was found to be suitable for mutant selection. Mutant with large colony size was selected and used to induce coenzyme Q_{10} production. In test tube with 5 mL seed medium (per 100 mL medium: sucrose 2.5 g, NH_4SO_4 1 g, K_2HPO_4 0.25 g, KH_2PO_4 0.2 g, $MgSO_4$ 0.05 g, yeast extract 1 g, peptone 1 g, $CaCl_2$ 0.02 g, SL 7 0.1 mL, pH 6.5) the chosen mutant was inoculated. It was incubated at 30ºC with constant shaking at 220 rpm. Seed culture (2.5%) was added to 20 mL production medium (same as seed medium) in a 100 mL flask and then incubated for 96 h at 30ºC with constant shaking at 220 rpm (Tokdar *et al.*, 2013).

Measurement of dry cell weight and extraction of CoQ_{10}

The 20 mL broth sample was centrifuged for 15 min at 6,000 rpm. The pellet was water-washed and dried at 60°C. The dry weight (DCW) of cell biomass was measured. Similarly, for extraction 20 mL harvested broth was centrifuged for 20 min at 1000 rpm to obtain biomass pellet, which was then extracted with 20 mL ethanol and heated in a water bath for 3 h at 60°C. Centrifugation was performed to separate the cells, and 20 mL hexane was used to extract the ethanol layer. Hexane layer was separated and concentrated to 1 mL (Tokdar *et al.*, 2013).

Quantification of CoQ10

For qualitative estimation, 20 µL extract was added to a silica gel plate using a spotter. Hexane: ethyl acetate (9:1) was used as mobile phase. High performance liquid chromatography (HPLC) (Sykam, S600 series) was used to measure CoQ_{10} using a silica column, where hexane: isopropyl alcohol (95:5) was utilized as mobile phase. The flow rate was 1 mL min^{-1} in isocratic mode and then detection was done at 275 nm. The CoQ_{10} enzyme (Sigma-C9538) was used as a standard (Tokdar *et al.*, 2013).

Optimization of media composition by RSM

We employed a second-order polynomial in this study in the manner described below:

$$Y = b0 + \Sigma bi\ Xi + \Sigma bii\ Xi2 + \Sigma\Sigma bij\ Xi\ Xj$$

where Xi, Xj, and Y are independent variables (or factors); the intercept, linear coefficient, quadratic coefficient, and interaction coefficient are denoted by the letters b0, bi, bii, bij, respectively.

RSM was used to optimize the starting concentration of five components for the manufacture of CoQ_{10}: the carbon source (sucrose), the nitrogen source (peptone and ammonium sulphate), and $MgSO_4$. The RSM was carried out utilizing a single level fractional central composite design (CCD) with four replicates of the central point in order to maximize the culture composition for CoQ_{10} synthesis. There were thirty runs in the experimental design. Sucrose (X1), ammonium sulphate (X2), peptone (X3), and $MgSO_4$ (X4) quantities were selected as independent factors, while response variables were selected to be CoQ_{10} level (mg g^{-1} DCW). The experiment design and data analysis were done using Design Expert software (version 7.0). The levels and ranges of experimental variables is given in Table 1. Using the Design Expert software, 30 experiments in total were created, and statistical analysis was done to assess the analysis of variance (ANOVA). It is important to highlight that this study used a 95% level of confidence.

RESULTS AND DISCUSSION

Regression analysis of experimental data

The CCD data and the responses for CoQ_{10} yield and DCW levels generated by *C. sphaeroides* GSPCDUBSR are given in Table 1. It revealed that the runs 15, 27, and 30 produced the highest levels (8.5 mg g^{-1} DCW) of CoQ_{10}.

The final equation in terms of coded factors was:

$$CoQ_{10} = +7.38 + 0.029*B + 0.29*D + 0.39*B^2 - 0.61*D^2$$

The final equation in terms of actual factors was:

$$CoQ_{10} = +5.84167 - 0.30354*\text{ammonium sulphate} + 10.96250*MgSO_4 + 0.015469*\text{ammonium sulphate}^2 - 9.81250*MgSO_4^2$$

Using ANOVA, the suitability of regression models was assessed. The ANOVA findings for CoQ_{10} production, derived from the equation are displayed in Tables 2 and 3. All the model terms were significant (P value < 0.05), according to these ANOVA tables. The response surface quadratic model was also significant as revealed by the F value of 3.99 and P value <0.05. The test of significance for regression coefficients of equation is presented in Table 4. Additionally, these table's P values attest that every model term is significant.

Optimal CoQ_{10} production range

The contour plots of CoQ_{10} production is presented in Fig. 1. These contour plots provide helpful details about the structure of interactions, in addition display the reciprocal interactions between the variables. For instance, in CoQ_{10} contour plots while all the possible interactions between different variables were linear, the interaction between $MgSO_4$ and ammonium sulphate gave a curve shape.

Fig. 2 displays the desirability values for the responses. In desirability function figure, the ideal values of various components are shown in brackets. Optimization study revealed 8.5 mg g^{-1} DCW of CoQ_{10}, on an average, occurred with the ideal culture composition of 30 g L^{-1} sucrose, 15 g L^{-1} ammonium sulphate, 25 g L^{-1} peptone, and 0.50 g L^{-1} $MgSO_4$.

RSM is one of the most popular statistical techniques employed for improving the fermentation process, which has lately drawn attention from several academics (Lv *et al.*, 2008; Godini *et al.*, 2017; Moghadami *et al.*, 2021). Numerous studies have focused

Table 1: Central composite design and responses for CoQ_{10} levels produced by *C. sphaeroides* GSPCDUBSR

Standard Number	Run	Sucrose (g L^{-1})	Ammonium sulphate (g L^{-1})	Peptone (g L^{-1})	Magnesium sulphate (g L^{-1})	CoQ_{10} yield (mg g^{-1} DCW)
27	1	30	10	25	0.5	6.8
30	2	30	10	25	0.5	6.6
7	3	25	15	30	0.25	7.3
18	4	40	10	25	0.5	7.5
24	5	30	10	25	1	7.1
5	6	25	5	30	0.25	7.5
9	7	25	5	20	0.75	7.2
6	8	35	5	30	0.25	8.3
21	9	30	10	15	0.5	6.9
4	10	35	15	20	0.25	8.1
12	11	35	15	20	0.75	6.1
3	12	25	15	20	0.25	7.5
22	13	30	10	35	0.5	6.5
29	14	30	10	25	0.5	7.2
19	15	30	0	25	0.5	8.5
1	16	25	5	20	0.25	7.2
8	17	35	15	30	0.25	7.8
28	18	30	10	25	0.5	7.6
13	19	25	5	30	0.75	7.3
14	20	35	5	30	0.75	6.5
25	21	30	10	25	0.5	6.4
17	22	20	10	25	0.5	8.1
15	23	25	15	30	0.75	7.3
10	24	35	5	20	0.75	6.6
20	25	30	20	25	0.5	8
16	26	35	15	30	0.75	8.2
2	27	35	5	20	0.25	8.5
23	28	30	10	25	0	23
26	29	30	10	25	0.5	26
11	30	25	15	20	0.75	11

Table 2: Regression analysis result obtained by ANOVA for the production of CoQ_{10}

Response 1: CoQ_{10}

Backward Elimination Regression with Alpha to Exit = 0.100

Removed	Coefficient estimate	t for H0 Coeff = 0	Prob >|t|	R-squared	MSE
C-Peptone	-0.013	-0.050	0.9611	0.5237	1.43
BC	0.019	0.063	0.9507	0.5236	1.34
B-NH_2SO_4	0.029	0.12	0.9033	0.5231	1.27
A-Sucrose	-0.038	-0.16	0.8723	0.5224	1.20
C^2	0.045	0.21	0.8330	0.5213	1.15
AB	-0.069	-0.26	0.7999	0.5197	1.10
CD	0.081	0.31	0.7592	0.5175	1.05
AC	0.16	0.61	0.5483	0.5093	1.02
BD	0.21	0.82	0.4228	0.4951	1.01
D-$MgSO_4$	0.29	1.40	0.1734	0.4537	1.05
AD	-0.38	-1.49	0.1486	0.4052	1.10
A^2	0.31	1.58	0.1253	0.3477	1.16

Table 3: Analysis of variance by ANOVA for the production of CoQ_{10}, ANOVA for response surface reduced quadratic model Analysis of variance table [Partial sum of squares – Type III]

Source	Sum of squares	Df	Mean square	F value	p-value	Prob > F
Model B	18.66	4	4.67	3.99	0.0123	significant
Amm. sulphate	0.020	1	0.020	0.017	0.8959	
D-$MgSO_4$	1.98	1	1.98	1.70	0.2047	
B^2	4.25	1	4.25	3.64	0.0681	
D^2	10.70	1	10.70	9.15	0.0057	
Residual	29.24	25	1.17			
Lack of Fit	28.03	20	1.40	5.80	0.0302	significant
Pure Error	1.21	5	0.24			
Cor Total	47.90	29				

Std. Dev.	1.08	R-Squared	0.3896
Mean	7.20	AdjR-Squared	0.2919
CV (%)	15.02	PredR-Square	-0.7972
PRESS	86.09	AdeqPrecisio	10.494

Table 4: Testing of the significance of the regression coefficients associated with CoQ_{10} production

Factor	Coefficient Estimate	Df	Standard Error	95%CI Low	95%CI High	VIF
Intercept	7.38	1	0.31	6.74	8.02	
B-NH_2SO_4	0.029	1	0.22	-0.43	0.48	1.00
D-$MgSO_4$	0.29	1	0.22	-0.17	0.74	1.00
B^2	0.39	1	0.20	-0.031	0.80	1.01
D^2	-0.61	1	0.20	-1.03	-0.20	1.01

on optimizing the CoQ_{10} production by different microbes using RSM statistical approach. Bule *et al.* (2009), for instance, used RSM method to assess the ideal levels of natural precursors that *Pseudomonas diminutra* could use to increase its CoQ_{10}production.Using RSM approach, the pH and soybean oil supplied to the culture media were optimized to produce CoQ_{10} by *Rhodotorula glutinis*. The findings demonstrated that inbatch and fed-batch cultures, the concentration of CoQ_{10} rose from 10 mg L^{-1} to 39.2 and 78.2 mgL^{-1}, respectively (Balakumaran and Meenakshisudaram, 2015). In a different study, Tian *et al.* (2010) used RSM to optimize the parameters including temperature, duration, and acid content that affected the lysis of *Agrobacterium tumefaciens* cells, and were able to double the extraction rates for CoQ_{10}. RSM has also conducted in a number of experiments to enhance the culture medium for *Gluconobacte*r strains (Hu *et al.*, 2012; Poljungreed and Boonyarattanakalin, 2017). A study by Wei *et al*. (2009) found that optimizing the media increased *G. oxydans* utilizing the Uniform Design (UD) approach where cell weight was also calculated. Wei *et al.* (2009) assessed different concentrations of sorbitol, yeast extract, ammonium sulphate, and KH_2PO_4 in culture media in combination with $MgSO_4$ using nine Uniform Design techniques, and achieved maximum cell weight by using 70 g L^{-1} sorbitol, 17.5 g L^{-1} yeast extract, 1.5 g L^{-1} ammonium sulphate, 1 g L^{-1} KH_2PO_4, and 0.2 g L^{-1} $MgSO_4$. They also reported KH_2PO_4 as the most crucial component in cell mass production. Moghadami *et al.* (2021) optimized ideal medium composition for boosting CoQ_{10} synthesis in *Gluconobacter japonicus* FM10 by using five different levels of sorbitol, yeast extract, peptone, KH_2PO_4, $MgSO_4$, and yeast extract by RSM. They achieved CoQ_{10} production of 3 mg L^{-1} when 110 g L^{-1} sorbitol, 25 g L^{-1} yeast extract, 35 g L^{-1} peptone, 0.5 g L^{-1} KH_2PO_4, and 0.55 g L^{-1} $MgSO_4$ were added to the culture medium. Nevertheless, there were differences in the recommended ideal culture compositions for DCW and CoQ_{10} synthesis. When compared to the other carbon and nitrogen sources, sorbitol and peptone were the most efficient for FM10 strain's synthesis of CoQ_{10} and DCW production. The most efficient sources of carbon and nitrogen in CoQ_{10} reportedly were sucrose and corn steep powder (Moghadami *et al.*, 2021). Adachi

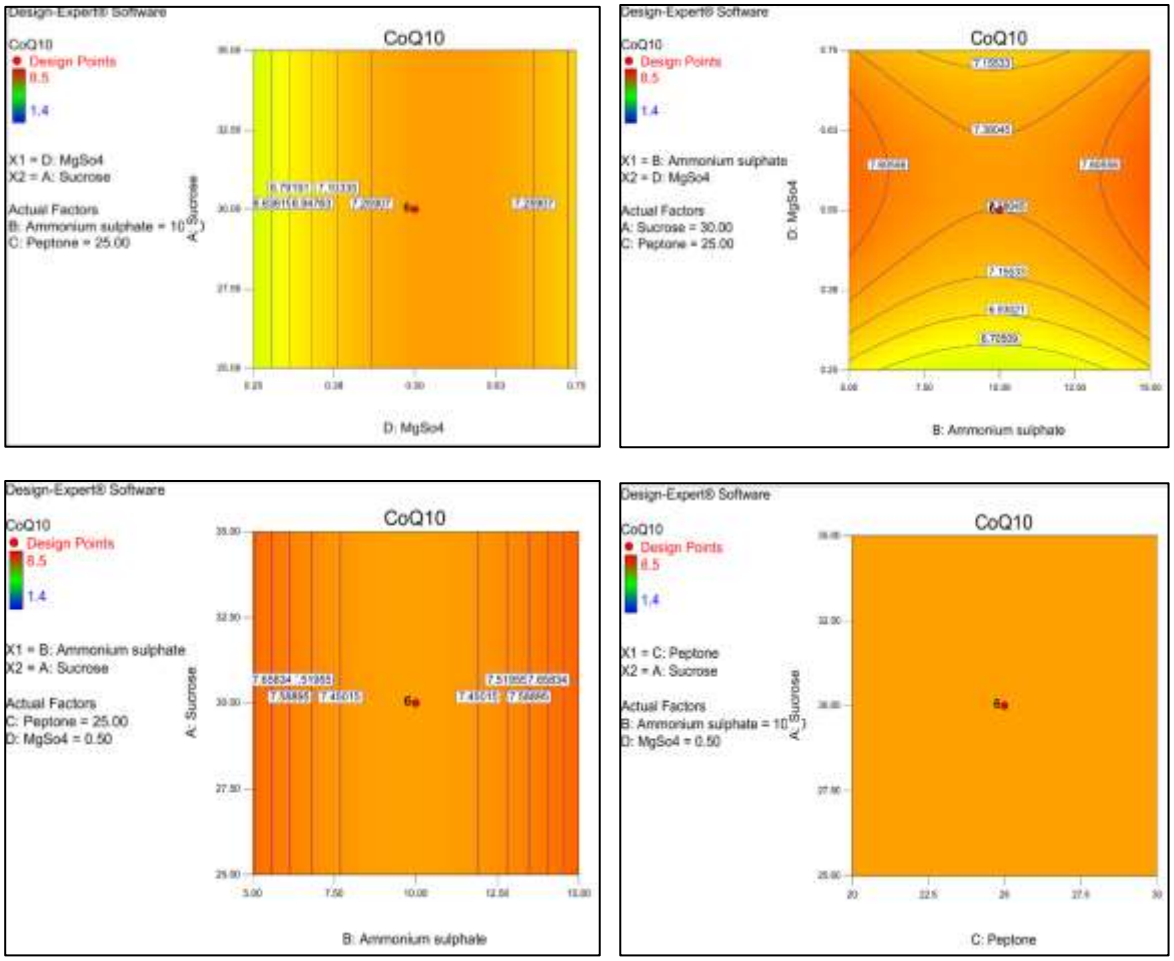

Fig. 1: Contour graphs of CoQ_{10} production

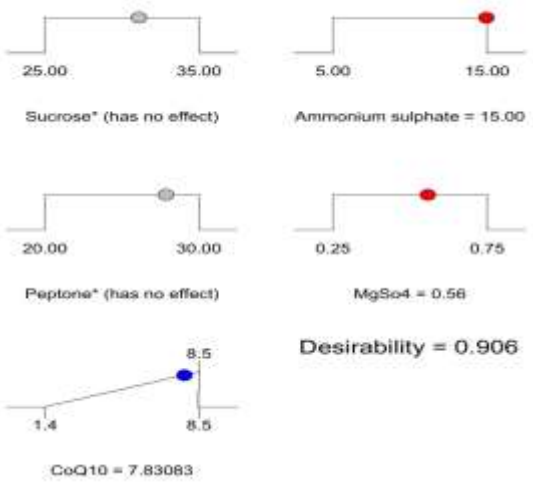

Fig. 2: Ramp plots showing the effect of the factors for CoQ_{10} production

et al. (2016) reported that the respiratory chain of *Gluconobacter* presumably uses membrane-bound dehydrogenases to oxidize D-sorbitol. Therefore, raising the concentration of sorbitol would increase the activity of dehydrogenases which, in turn, can increase DCW.

The RSM, which is a set of statistical and mathematical techniques, offers a statistically sound and effective approach to analysis and does not have the drawbacks such as that of the Taguchi method. The adjusted coefficient of determination, represented by Adjusted R^2, was used to assess the quality of fitted models. As is often known, these values between 0 and 1 suggest that the related regression model can be applied as a suitable response variable predictor. In present study, 0.2919 was the representative Adjusted R^2 (Table 3). The comparatively value of adjusted R^2suggest that the suggested regression models are capable of forecasting the CoQ_{10}synthesis. The models' F-values were significant (P value < 0.05), confirming

the suggested models' applicability. Additionally, all model terms were significant, according to the P values (P value < 0.05).

In conclusion, the optimization using RSM yielded 8.5 mg g^{-1} DCW of CoQ_{10} on an average with the ideal culture condition of 30 g L^{-1} sucrose, 15 g L^{-1} ammonium sulphate, 25 g L^{-1} peptone, and 0.50 g L^{-1} $MgSO_4$, which is signification improvement thus demonstrating the applicability of the RSM technique in fermentation optimization studies.

Conflict of interest: The authors declare that there is no conflict of interest regarding the publication of this paper.

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Author's contribution: BS performed the experiments. MT wrote the manuscript. SVR edited the manuscript, GS designed the experiments, reviewed the manuscript for final publication.

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