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Short Communication:

Multiple Response Optimization of an HPLC Method for Analyzing Resorcinol and 4-*n*-Butyl Resorcinol in Lipid Nanoparticles

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Abstract: Resorcinol and 4-*n*-butyl resorcinol have been used to improve skin health. However, these two compounds were unstable due to the oxidation process. Lipid nanoparticle formulation strategies were reported as the solution to overcome the stability problem for both resorcinol and 4-*n*-butyl resorcinol. Nevertheless, it is important to determine the content of resorcinol and 4-*n*-butyl resorcinol in lipid nanoparticle formulation. Aiming to develop the analytical method for resorcinol and 4-*n*-butyl resorcinol determination, a response surface methodology (RSM) was applied in the HPLC optimization stage. An optimized HPLC condition was obtained by generating a Box-Behnken design followed by multiple response analysis. It was obtained that optimized HPLC conditions due to the predictive multiple response optimization were methanol percentage of 50.0%, acetonitrile percentage of 18.1%, and flow rate of 0.6 mL min⁻¹. This optimized condition was successfully applied and met the requirements of the system suitability test. Quantitative estimation was performed and resulted that the resorcinol and 4-*n*-butyl resorcinol content in lipid nanoparticles were 70.37 ± 0.47 and 95.07 ± 0.80 µg mL⁻¹, respectively.

Keywords: 4-*n*-butyl resorcinol; Box-Behnken design; HPLC; optimization; resorcinol

■ INTRODUCTION

Resorcinol (benzene-1,3-diol) has been widely used in the formulation of drugs and cosmetics. Resorcinol was formulated as an ointment for skin therapy and medication for acne, seborrheic dermatitis, eczema, psoriatic, and other skin health problems [1]. 4-*n*-Butyl resorcinol, a resorcinol derivative, can be used in melisma therapy [2]. This hygroscopic compound was unstable in the room temperature storage by resulting in a color change. The discoloration of resorcinol and 4-*n*-butyl resorcinol (Fig. 1) can be occurred due to the oxidation process [3]. In the previous study, the physical stability of 4-*n*-butyl resorcinol towards the oxidation process can be enhanced by lipid nanoparticle formulation [4].

Nanoparticles were described as small particles with a size of < 200 nm [5]. In recent years, nanoparticle technology was applied to health since it provided a significant contribution in the drug delivery and therapeutic system [6]. A Lipid nanoparticle, a nanoparticle system that consists of phospholipid molecules, has several advantages, such as lower toxicity, ability to improve drugs' physical properties, flexibility

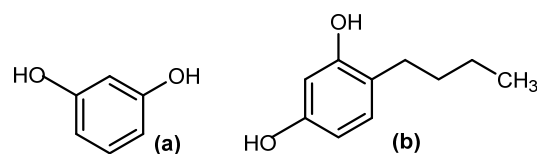


Fig 1. Chemical structures of resorcinol (a) and 4-*n*-butyl resorcinol (b)

to combine hydrophilic and lipophilic properties, stability enhancer, and supporting the drug release in a specific target [7]. Hence, it is possible to improve the stability of 4-*n*-butyl resorcinol by applying lipid nanoparticle formulation [4].

There was a need to determine the content of resorcinol and 4-*n*-butyl resorcinol in the lipid nanoparticle in order to control the quality of the pharmaceutical dosage form. Several modern multivariate analysis techniques for quantitatively determining analytes content in mixtures were applied to analyze food and drug materials [8-10] as well as herbal products [11-13]. However, it is necessary to develop chromatographic separation for determining 'actual value' for chemometrics modeling prediction [14-15]. In the last decade, chromatography techniques have been widely applied to determine chemicals content in foods [16-19], drugs [20-22], and herbals [23-26]. High-performance liquid chromatography (HPLC) can be applied in drug analysis in different matrices and mixtures. There were several publications about resorcinol analysis, but the reported study of resorcinol and 4-*n*-butyl resorcinol determination using HPLC was limited [27-31]. Hence, it is important to develop an appropriate HPLC method as well as its separation condition to analyze resorcinol and 4-*n*-butyl resorcinol in lipid nanoparticles.

Optimization of separation conditions is a crucial stage in analytical method development [32-34]. Chemometrics-assisted chromatographic optimization can be performed using response surface methodologies (RSM) such as factorial, central composite (CCD), Box-Behnken (BBD), and Doehlert designs [35]. The BBD was developed from the design factorial model [36], which has model characteristics of rotatable with three levels for each experimental factor [37]. This design was more effective and economical than other three-level designs [38], with fewer experimental runs compared to full factorial or CCD [39]. In addition, BBD was commonly applied in several studies of HPLC method development [40-43].

The aim of this study was to develop an HPLC method for a simultaneous determination of resorcinol

and 4-*n*-butyl resorcinol in lipid nanoparticles. We reported a new optimization model for separating resorcinol and 4-*n*-butyl resorcinol in lipid nanoparticles by HPLC method using a chemometrics approach. BBD was performed to achieve the optimized condition of mobile phase composition of methanol and acetonitrile percentages as well as its flow rate adjustment. Multiple response analysis was conducted to obtain the optimized condition among nine different experimental responses.

■ EXPERIMENTAL SECTION

Materials

Resorcinol standard was purchased from Sigma Aldrich, while 4-*n*-butyl resorcinol standard was purchased from TCI. Solvents used in this study were methanol, acetonitrile (gradient grade for liquid chromatography, Merckmillipore), soy lecithin (Nacalai), and redistilled water (PT. Ikapharmindo Putramas). Lipid nanoparticle was produced in the Faculty of Pharmacy, Sanata Dharma University, Indonesia [43].

Instrumentation and Software

Instrumentation used in this study were HPLC system of Shimadzu® LC-2010 CHT with UV/Vis detector, C18 column of Luna Phenomenex® (250 × 4.6 mm i.d., 5 µm), ultra-micro analytical balance RADWAG® series of UYA 2.3Y (max. 2.1 g, min. 0.01 mg), Scaltec® SBC 22 analytical balance (max. 60/210 g, min. 0.001 g), Gast® vacuum pump model DOA-P504-BN, Retsch® T460 ultrasonicator, sterile syringe filter with a 0.2 µm pore size hydrophilic PTFE membrane (Merckmillipore), and a set of Socorex® micropipettes. Response surface methodology and multiple response optimization were performed using Minitab® 19 for Windows.

Procedure

Standard solution and sample preparation

The resorcinol stock solution was prepared by accurately weighing 1.079 mg resorcinol, transferred into a 5 mL volumetric flask, and diluting into the volume. Meanwhile, a 4-*n*-butyl resorcinol stock solution was prepared by accurately weighing 8.200 mg

4-*n*-butyl resorcinol, transferred into a 10 mL volumetric flask, and then followed by dilution into the volume. Resorcinol and 4-*n*-butyl resorcinol working solutions were prepared by transferring 0.500 and 0.122 mL of resorcinol and 4-*n*-butyl resorcinol stock solution, respectively, into separate 5 mL volumetric flask followed by dilution into the volume. The standard mixture solution was prepared by mixing 0.500 and 0.122 mL of resorcinol and 4-*n*-butyl resorcinol stock solution into a 5 mL volumetric flask followed by dilution into the volume. The sample solution was prepared by transferring 0.5 mL sample solution of soy lecithin lipid nanoparticles containing resorcinol and 4-*n*-butyl resorcinol into a 5 mL volumetric flask followed by dilution into the volume. All solutions were filtered using a sterile syringe filter membrane before injection into the HPLC system.

Response surface methodology

HPLC system optimization was performed by applying the response surface methodology. The preliminary HPLC optimization method in this study was carried out using one variable at time (OVAT) technique. The BBD was applied to observe three different independent variables, namely methanol percentage (X1), acetonitrile percentage (X2), and flow rate (X3). Table 1 presented independent variables with three different levels for generating the BBD model. This experimental design was executed by observing 16 runs, including 12 runs at BBD points and 4 runs at central points.

Multiple response optimization

Dependent variables in this study were separation properties for both resorcinol and 4-*n*-butyl resorcinol (retention time, resolution, tailing factor, and the number of theoretical plates) and HPLC column pressure. It was necessary to perform the multiple response optimization since there were nine different dependent variables with

different goals (maximum or minimum) for each variable. This computational optimization process was carried out by employing the response optimizer in Minitab software.

System suitability test

System suitability test was performed in this study to assess recommended optimization setting resulted from the multiple response optimization stages. Ten microliters of standard mixture solution containing resorcinol and 4-*n*-butyl resorcinol were injected in HPLC system and replicated five times.

Quantitative estimation

Quantitative estimation for resorcinol and 4-*n*-butyl resorcinol were performed using multiple-point calibration method. Each compound's calibration graph was constructed and applied in the quantitative determination for both resorcinol and 4-*n*-butyl resorcinol.

RESULTS AND DISCUSSION

Response Surface Methodology

The optimization of HPLC system was necessary to obtain appropriate conditions for achieving sophisticated separation during the analytical process. The preliminary optimization method was carried out using OVAT technique. Three variations of HPLC condition, including the percentage of methanol, percentage of acetonitrile, and flow rate, were applied in the system, followed by the chromatogram observation. Fig. 2 presented three OVAT variations, namely OVAT1, OVAT2, and OVAT3. It was found that OVAT1 and OVAT2 with 70% methanol and 20% acetonitrile in the mobile phase resulted in the separation of both resorcinol and 4-*n*-butyl resorcinol with the retention time less than 10 min. However, the flow rate of 0.8 mL min⁻¹ (OVAT1) resulted in a tailing profile for resorcinol peak, while a flow rate of 0.6 mL min⁻¹ (OVAT2) resulted in a tailing profile resorcinol peak and baseline drift. In OVAT3 with 50% methanol and 20% acetonitrile in the mobile phase and flow rate of 0.6 mL min⁻¹ resulted in better peaks separation with the retention time of 4-*n*-butyl resorcinol was more than 10 min. These OVAT observations were considered to

Table 1. Experimental variables with three levels for response surface methodology

Variables	Levels		
	Low	Medium	High
X1: Methanol (%)	50	60	70
X2: Acetonitrile (%)	10	15	20
X3: Flow rate (mL min ⁻¹)	0.6	0.7	0.8

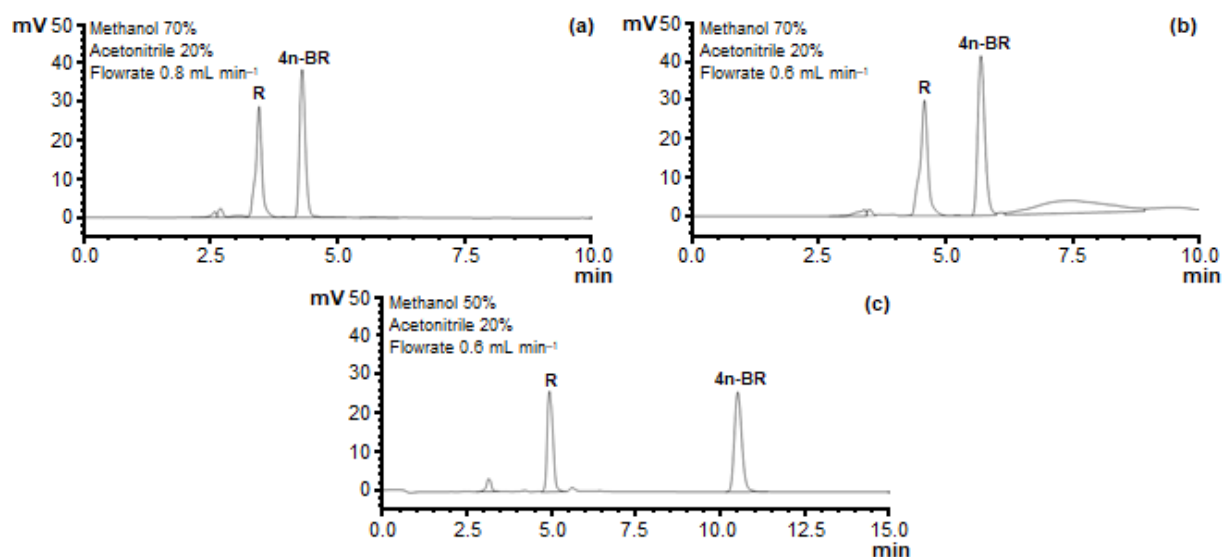


Fig 2. Preliminary HPLC optimization using three variations separation condition of OVAT1 (a), OVAT2 (b), and OVAT3 (b) for standard solution mixture containing resorcinol (R) and 4-*n*-butyl resorcinol (4-*n*-BR). Column: C18 column of Luna Phenomenex® (250 × 4.6 mm i.d., 5 µm). Wavelength detection at 279 nm. Volume injection: 10 µL

Table 2. The Box-Behnken design with experimental responses of resorcinol and 4-*n*-butyl resorcinol separation

Run	X1	X2	X3	Resorcinol				4- <i>n</i> -butyl resorcinol				Press.
				ret	res	tai	N	ret	res	tai	N	
1	50	10	0.7	4.613	8.334	1.270	4484	17.116	27.685	1.138	11900	208
2	70	10	0.7	4.049	4.468	1.191	4613	6.315	6.312	1.215	7233	190
3	50	20	0.7	4.277	5.792	1.153	3928	9.158	15.015	1.188	9430	185
4	70	20	0.7	3.937	3.323	0.989	5146	4.917	4.249	1.227	6623	144
5	50	15	0.6	5.148	6.347	1.103	4214	14.142	21.031	1.177	11053	187
6	70	15	0.6	4.643	4.342	0.884	5574	6.374	6.344	1.240	7367	161
7	50	15	0.8	3.874	5.309	1.105	3928	10.653	20.044	1.163	9861	231
8	70	15	0.8	3.496	3.234	1.034	4562	4.814	5.897	1.209	6437	185
9	60	10	0.6	4.957	5.285	1.283	4433	11.129	16.297	1.193	9382	195
10	60	20	0.6	4.722	4.374	1.267	4989	7.323	6.287	1.219	8003	160
11	60	10	0.8	3.750	4.981	1.278	4063	8.365	15.399	1.176	8448	241
12	60	20	0.8	3.557	4.149	1.261	4265	5.516	5.764	1.291	5887	204
13	60	15	0.7	4.143	7.584	1.288	3862	7.541	11.24	1.219	7969	196
14	60	15	0.7	4.141	7.771	1.298	3872	7.532	11.234	1.218	7975	196
15	60	15	0.7	4.140	7.674	1.300	3805	7.525	9.664	1.215	7944	196
16	60	15	0.7	4.138	7.550	1.300	3789	7.519	11.139	1.216	7912	196

Note: X1: methanol percentage (%); X2: acetonitrile percentage (%); X3: flow rate (mL min⁻¹); ret: retention time (min); res: resolution; tai: tailing factor; N: theoretical plate number; Press: pressure (kgf cm⁻²)

develop further optimization stages with the application of RSM. BBD, one of the RSM techniques, has been chosen to optimize HPLC separation conditions since it provided an effective and economic statistical model for optimization purposes [38]. Three levels and three factors

BBD model was generated using Minitab software. Methanol percentage, acetonitrile percentage, and flow rate were stated as independent variables of the experiment. While retention time, resolution, tailing factor, and the number of theoretical plates for both

resorcinol and 4-*n*-butyl resorcinol were stated as dependent variables of the chromatographic separation experiment. Column pressure was also stated as the dependent variable since it was important to maintain the separation process and column lifetime. Table 2 presented independent variables and dependent variables as well as their results from 16 runs of BBD model for separating resorcinol and 4-*n*-butyl resorcinol.

Experimental results of BBD observation were analyzed to obtain statistical information for further method optimization. Table 3 presented RSM analytical results of resorcinol and 4-*n*-butyl resorcinol separation, including regression equation, R^2 , adjusted R^2 , and p-value. It should be noted that independent variables are significantly affected if the value of $R^2 \geq 0.8$ and adjusted $R^2 > 0.8$, while the difference between R^2 and adjusted R^2

must be less than 0.2 [41]. The response of 4-*n*-butyl resorcinol tailing factor has an R^2 of 0.888 and an adjusted R^2 of 0.720. However, all p-values results were less than 0.05 and considered to be statistically significant [33]. Hence, we decided to include all the nine responses to be analyzed further in the multiple response optimization stages.

Multiple Response Optimization

All responses, including retention time, resolution, tailing factor, and the number of theoretical plates for both resorcinol and 4-*n*-butyl resorcinol, and the column pressure, were considered to build model prediction for HPLC separation. Its because they were indicated statistically significant due to their p-values. The goal for retention time, tailing factor, and column

Table 3. Response surface methodology analytical results of resorcinol and 4-*n*-butyl resorcinol separation

Responses	Regression Equation in Uncoded Units	R^2	R^2 (adj)	p-Value
Resorcinol retention time	$Y = 19.265 - 0.13471 X_1 - 0.12465 X_2 - 20.619 X_3 + 0.000611 X_1^*X_1 + 0.000695 X_2^*X_2 + 8.862 X_3^*X_3 + 0.001120 X_1^*X_2 + 0.03175 X_1^*X_3 + 0.02100 X_2^*X_3$	0.999	0.999	0.000
Resorcinol resolution	$Y = -110.1 + 1.010 X_1 + 0.783 X_2 + 250.4 X_3 - 0.01027 X_1^*X_1 - 0.04552 X_2^*X_2 - 180.9 X_3^*X_3 + 0.00699 X_1^*X_2 - 0.018 X_1^*X_3 + 0.039 X_2^*X_3$	0.966	0.914	0.001
Resorcinol tailing factor	$Y = -7.17 + 0.2057 X_1 - 0.0399 X_2 + 8.01 X_3 - 0.001933 X_1^*X_1 + 0.001900 X_2^*X_2 - 7.17 X_3^*X_3 - 0.000425 X_1^*X_2 + 0.0370 X_1^*X_3 - 0.0005 X_2^*X_3$	0.945	0.863	0.004
Resorcinol plate number	$Y = 31827 - 419 X_1 - 532 X_2 - 33702 X_3 + 4.214 X_1^*X_1 + 11.57 X_2^*X_2 + 31612 X_3^*X_3 + 5.44 X_1^*X_2 - 181.5 X_1^*X_3 - 177 X_2^*X_3$	0.967	0.918	0.001
4- <i>n</i> -butyl resorcinol retention time	$Y = 156.4 - 2.844 X_1 - 3.264 X_2 - 60.3 X_3 + 0.01380 X_1^*X_1 + 0.01869 X_2^*X_2 + 8.7 X_3^*X_3 + 0.03280 X_1^*X_2 + 0.482 X_1^*X_3 + 0.479 X_2^*X_3$	0.993	0.982	0.000
4- <i>n</i> -butyl resorcinol resolution	$Y = 219.0 - 4.585 X_1 - 4.24 X_2 - 23.7 X_3 + 0.02444 X_1^*X_1 + 0.0021 X_2^*X_2 + 6.6 X_3^*X_3 + 0.0530 X_1^*X_2 + 0.135 X_1^*X_3 + 0.19 X_2^*X_3$	0.991	0.977	0.000
4- <i>n</i> -butyl resorcinol tailing factor	$Y = 0.411 + 0.0371 X_1 - 0.0132 X_2 - 0.96 X_3 - 0.000238 X_1^*X_1 - 0.000050 X_2^*X_2 + 0.400 X_3^*X_3 - 0.000190 X_1^*X_2 - 0.00425 X_1^*X_3 + 0.0445 X_2^*X_3$	0.888	0.720	0.028
4- <i>n</i> -butyl resorcinol plate number	$Y = 56770 - 1325 X_1 - 378 X_2 + 8060 X_3 + 7.980 X_1^*X_1 + 1.94 X_2^*X_2 - 6850 X_3^*X_3 + 9.30 X_1^*X_2 + 65.5 X_1^*X_3 - 591 X_2^*X_3$	0.995	0.986	0.000
Pressure	$Y = -233 + 17.54 X_1 + 7.22 X_2 - 415 X_3 - 0.1162 X_1^*X_1 - 0.1050 X_2^*X_2 + 662 X_3^*X_3 - 0.1150 X_1^*X_2 - 5.00 X_1^*X_3 - 1.00 X_2^*X_3$	0.991	0.977	0.000

pressure were expected to be the minimum value. In contrast, the goal for resolution and theoretical plate numbers were expected to be the maximum value.

General optimization considering all significant factors was generated by calculating the desirability function computed by Minitab software. Desirability calculation resulted in a value with a scale between 0–1. Desirability value of 0 represents a completely undesirable response while 1 represents the most desirable response [44]. Overall desirability in this study was 0.444 indicated several errors in the prediction model. It was found that HPLC system settings due to the predictive multiple response optimization were methanol percentage of 50.0%, acetonitrile percentage of 18.1%, and flow rate of 0.6 mL min⁻¹. Table 4 presented multiple response optimization for resorcinol and 4-*n*-butyl resorcinol along with prediction value for each response and percentage of errors compared with the observational values. Except for resorcinol resolution and plate numbers, all predictions resulted in a minimum error (< 5%) and indicated a good correlation between prediction responses and observational responses [45]. The unexpected percentage of error more than 10% for resorcinol theoretical plate number and a very high percentage of error for resorcinol resolution may contribute to the overall desirability value

of 0.444. However, the HPLC peak separation quality will increase with the higher value of resolution [46]. Hence, it was important to perform a system suitability test with the HPLC system suggested by the multiple response optimization models.

System Suitability Test

HPLC system suggestion as an output from the multiple response optimization should be applied to confirm its performance toward analytes separation. For this purpose, HPLC separation properties, including retention time (RT), peak area, resolution (Rs), peak tailing factor (TF), theoretical plate number (N), and column pressure, were assessed in the system suitability test. Table 5 presented the results of the system suitability test. It was found that the system suitability test was met the requirements since the relative standard deviation (RSD) was < 2.0, resolution value greater than 2.0, tailing factor near 1.0, and theoretical plate number more than 2000 [46]. The retention time of 4-*n*-butyl resorcinol of 11.540 min was still acceptable since all analytes can be detected before 15 min while maintaining column pressure of 188 kgf cm⁻². Fig. 3 depicted HPLC separation of resorcinol and 4-*n*-butyl resorcinol under the optimized condition. Chromatogram profiles of solvent, standard

Table 4. Multiple response optimization for resorcinol and 4-*n*-butyl resorcinol

Responses	Optimization parameters				Prediction	Error (%)
	Goal	Lower	Target	Upper		
Resorcinol retention time	Minimum	-	3.5	5.148	4.793	4.67
Resorcinol resolution	Maximum	3.23	8.3	-	6.231	87.17
Resorcinol tailing factor	Minimum	-	0.9	1.3	1.154	4.91
Resorcinol plates number	Maximum	3789	5574	-	4095.7	10.94
4- <i>n</i> -butyl resorcinol retention time	Minimum	-	4.8	17.116	11.504	0.31
4- <i>n</i> -butyl resorcinol resolution	Maximum	4.25	27.7	-	16.947	2.61
4- <i>n</i> -butyl resorcinol tailing factor	Minimum	-	1.1	1.291	1.175	1.09
4- <i>n</i> -butyl resorcinol plates number	Maximum	5887	11900	-	10335.9	1.02
Pressure	Minimum	-	144	241	179	4.79

Note: Desirability value (D) = 0.444

Table 5. Results of system suitability test (n = 5)

Analytes	RT		Area		Rs	TF	N	Pressure (kgf cm ⁻²)
	Mean (min)	RSD (%)	Mean	RSD (%)				
Resorcinol	5.028	0.128	111899.2	0.525	3.329	1.100	4598.6	188
4- <i>n</i> -butyl resorcinol	11.540	0.563	153598.4	1.275	17.402	1.188	10442.8	

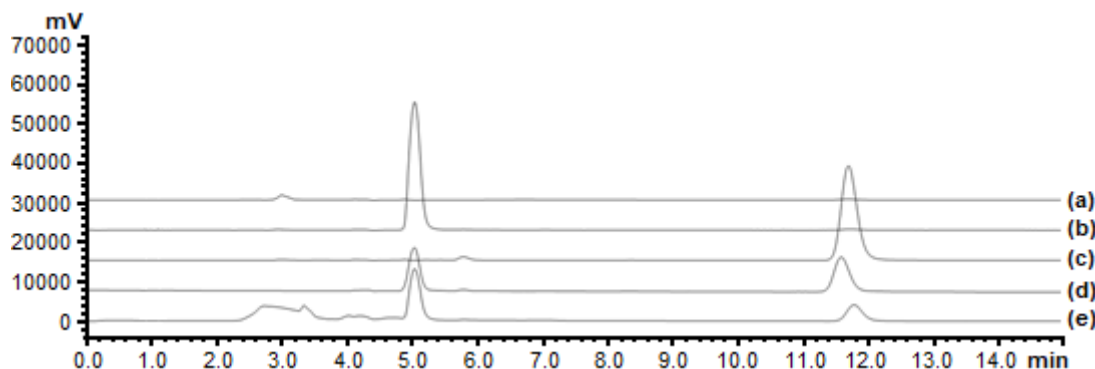


Fig 3. Representative HPLC chromatograms of methanol as solvent (a), standard solution of resorcinol (b), standard solution of 4-*n*-butyl resorcinol (c), standard solution mixture containing resorcinol and 4-*n*-butyl resorcinol (d), and lipid nanoparticle sample solution (e). Mobile phase: methanol-acetonitrile-water (50.0:18.1:31.9 v/v). Flow rate: 0.6 mL min⁻¹. Column: C18 column of Luna Phenomenex® (250 × 4.6 mm i.d., 5 µm). Wavelength detection at 279 nm. Volume injection: 10 µL

of resorcinol, standard of 4-*n*-butyl resorcinol, a mixture of standard solution, and sample lipid nanoparticles were exhibited in a stacked arrangement.

Quantitative Estimation

HPLC optimization followed by quantitative estimation was previously reported using single-point calibration [32,47]. In this study, a multiple-point calibration method was applied for estimating the content of resorcinol and 4-*n*-butyl resorcinol. The calibration equations for resorcinol and 4-*n*-butyl resorcinol were $y = 17819x - 13223$ ($R^2 = 0.994$) and $y = 22148x - 57082$ ($R^2 = 0.998$), respectively. It was found that contents of resorcinol and 4-*n*-butyl resorcinol in lipid nanoparticle samples ($n = 6$) were 70.37 ± 0.47 and 95.07 ± 0.80 µg mL⁻¹.

CONCLUSION

An HPLC method development to analyze resorcinol and 4-*n*-butyl resorcinol in lipid nanoparticle samples has been successfully conducted. Multiple response optimization was applied to obtain the optimized HPLC condition for methanol and acetonitrile percentage of the mobile phase as well as the flow rate. System suitability test was performed to confirm the HPLC performance for separation purpose followed by quantitative estimation of these two analytes. In the future, we plan to perform analytical method validation for the next stage of our lipid nanoparticles research to

achieve comprehensive information both for optimization and validation of the HPLC method.

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