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Optimisation of Ibuprofen Extraction by Emulsion Liquid Membrane Using Box-Behnken Design

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ABSTRACT: *Emulsion liquid membrane (ELM) is a potential method for extracting ibuprofen (IBP) from aqueous solution. The concentrations of the carrier, surfactant and internal phases are important parameters to optimise the extraction efficiency of IBP. The Box-Behnken design (BBD) is used to optimise the main parameters of ELM, which are Aliquat 336 (A), Span 80 (B) and sodium carbonate, Na_2CO_3 (C). The responses were calculated using quadratic polynomial regression and the model suggests a significant result with the experimental data set, with the F-value and p-value calculated at 17.88% and 0.05%, respectively. Span 80 and Na_2CO_3 had a mutual interaction which was significant for the IBP extraction by ELM. At the optimised parameters, namely Aliquat 336 concentration (2 wt%), Span 80 concentration (4 wt%) and Na_2CO_3 concentration (0.1 M) resulted in 96.78% of IBP extraction.*

Keywords: ibuprofen, emulsion liquid membrane, response surface methodology, Box-Behnken design

1. INTRODUCTION

Emulsion liquid membrane (ELM) is an alternative treatment method for removing solutes of interest from contaminated sources. Along with its low chemical consumption, larger contact surface area per volume and energy efficiency, ELM has significant potential in a wide range of applications. Various ELM studies have been reported for the recovery of heavy metals, phenolic compound, dyes and pharmaceuticals.[1–6] ELM is a solvent-dissolved mixture of a carrier, a surfactant and an internal phase. The carrier facilitates the transport of the solute from the feed phase, whereas the internal phase acts as a stripping agent to strip the extracted solute.[7] Surfactants act as emulsifiers to stabilise the water-in-oil emulsion (O/W) or oil-in-water emulsion (W/O). Ahmad et al. reported that carrier, surfactant and internal phase concentration can alter the extraction efficiency of ELM.[5]

Response surface methodology (RSM) is an empirical statistical tool for modelling the response surface using a multivariable. RSM has the advantage of reducing laboratory work and significantly lowering chemical consumption.[8] This method has been widely employed in optimising chemical factors in many process fields such as liquid-liquid extraction, chemical oxidation, precipitation process and sol-gel method.[9–14] Among RSM, Box-Behnken design (BBD) is more commonly used in ELM because it requires fewer experimental runs. Number of literatures have been found on the application of BBD for removal of targeted solute using ELM.[15–17]

Previous work reported on the effect of important parameters during the screening of ELM for IBP removal from aqueous solution.[18] During the screening, authors discovered that an ELM formulation consisted of Aliquat 336 (carrier), Span 80 (surfactant) and sodium bicarbonate, Na_2CO_3 (internal phase) has achieved high extraction efficiency. However, the previous work did not analyse the interaction among the experimental parameters. Thus, the objective of the current manuscript is the continuation of the previous work whereby to optimise and analyse the interactive effect of the main ELM parameters such as carrier concentration, surfactant concentration and stripping agent concentration on IBP extraction using BBD. This optimisation and statistical analysis have the potential to predict IBP extraction efficiency in a variety of experimental settings.

2. EXPERIMENTAL DESIGN

Experimental procedure of emulsion preparation and extraction followed the previous publication.[18] Equation (1) denoted the experimental extraction efficiency, E (%) where C_f and C_i is the final and initial concentration of IBP in the feed phase. BBD is an experimental design tool for generating higher order response surfaces with a small number of runs. BBD is commonly used in ELM to optimise extraction performance by studying the effect and interaction of several parameters that may give a high response to the extraction.[19] The carrier concentration (1 wt%, 2 wt% and 3 wt%), surfactant concentration (2 wt%, 4 wt% and 6 wt%)

and internal phase concentration (0.05 M ,0.1 M and 0.15 M) have been selected for optimisation using BBD. The selection of these value range is based on the previous work for carrier, surfactant and internal phase concentration.[1,4,5,20,21] The literatures aforementioned claimed that all of the three parameters have major contribution to the extraction efficiency of targeted solute from the feed phase. Table 1 shows the range of individual factors.

$$E\,(\%) = \frac{C_i - C_f}{C_i} \times 100 \quad (1)$$

Table 1: Range of carrier, surfactant and internal phase for BBD

Factors	Range		
Aliquat 336 (wt%)	1	2	3
Span 80 (wt%)	2	4	6
Na_2CO_3 (M)	0.05	0.10	0.15

3. RESULT AND DISCUSSION

3.1 Quadratic Polynomial Model of BBD

A 3-level BBD developed by Design Expert 13 software can be used to compute the parameters of concentration of carrier, surfactant and internal phase. A total of 17 experiments needs to be carried out to determine the responses (extraction efficiency in %) based on orthogonal 2^3 BBD with five replicates at centre point, all in duplicates. All the BBD experiments were run in batch to determine the extraction efficiency of IBP. The software's quadratic model is used to calculate the predicted extraction efficiency, as shown in the following regression Equation (2):

$$E_{\text{predicted}}\,(\%) = \begin{array}{l} 19.12012 + 22.95804A + 1.78852B \\ + 1135.86627C - 1.09143AB - 60.10728AC \\ + 70.46161BC - 3.43972A^2 - 0.820277B^2 \\ - 6954.98767C^2 \end{array} \quad (2)$$

Where A, B and C is denoted as Aliquat 336 concentration, Span 80 concentration and Na_2CO_3 concentration, respectively. $E_{\text{predicted}}$ is determined by the role of parameter A, B, C and interaction between parameters. The value of regression coefficient (R^2 = 0.9583) indicates the correlation is significant to predict the extraction of IBP. Hence, the predicted value is found to be closer to the experimental results. Table 2 displays the experimental and predicted extraction efficiencies for each of the 17 experiments. Based on run 1, $E_{predicted}$ of IBP is 96.78% while the residual is calculated based on the difference between the E (%) and $E_{predicted}$. The same calculation of $E_{predicted}$ and its residual is applied for other subsequent run.

Table 2: BBD of experimental and predicted extraction efficiencies of IBP.

Run	A	B	C	E (%)	$E_{predicted}$ (%)	Residual
1	2	4	0.10	96.30	96.78	−0.48
2	3	4	0.05	83.54	82.45	1.09
3	2	6	0.15	82.64	78.66	3.99
4	1	4	0.15	74.37	75.46	−1.09
5	2	4	0.10	96.95	96.78	0.17
6	2	2	0.15	65.08	64.21	0.87
7	2	2	0.05	83.66	87.65	−3.99
8	1	2	0.10	89.08	88.87	0.22
9	2	4	0.10	97.23	96.78	0.45
10	1	6	0.10	90.70	93.59	−2.90
11	3	6	0.10	86.66	86.87	−0.21
12	3	2	0.10	93.78	90.88	2.90
13	2	4	0.10	96.44	96.78	−0.34
14	1	4	0.05	82.57	78.80	3.77
15	3	4	0.15	63.32	67.09	−3.77
16	2	4	0.10	96.96	96.78	0.19
17	2	6	0.05	73.04	73.91	−0.87

3.2 Analysis of Variance

The analysis of variance (ANOVA) of the BBD quadratic model of extraction IBP is shown in Table 3. ANOVA is used to determine the model's significance and adequacy. The mean squares is computed by dividing the sum of the squares of the two source variations, model and error variance, by the degree of freedom variations.[21] The F-value quantifies the variation of experimental data toward the experimental mean, whereas the p-value indicates the significance of the F-value.

Table 3: Analysis of variance of BBD quadratic model for extraction of IBP.

Source	Sum of squares	df	Mean square	*F*-value	*p*-value	
Model	1876.41	9	208.49	17.88	0.0005	Significant
A-Aliquat 336	11.09	1	11.09	0.9509	0.3620	
B-Span 80	0.2570	1	0.2570	0.0220	0.8862	
C-Na_2CO_3	174.84	1	174.84	15.00	0.0061	
AB	19.06	1	19.06	1.63	0.2418	
AC	36.13	1	36.13	3.10	0.1218	
BC	198.59	1	198.59	17.03	0.0044	
A^2	49.82	1	49.82	4.27	0.0776	
B^2	45.33	1	45.33	3.89	0.0893	
C^2	1272.94	1	1272.94	109.17	< 0.0001	
Residual	81.62	7	11.66			
Lack of fit	81.00	3	27.00	175.81	0.0001	Significant
Pure error	0.6143	4	0.1536			
Cor. total	1958.03	16				

Notes: SD = 3.41; mean = 85.43; coefficient of variation % = 4; $R^2 = 0.9583$*; adjusted* $R^2 = 0.9047$*; predicted* $R^2 = 0.3376$*; adequate precision = 12.436.*

Based on Table 3, the model has *F*-value of 17.88, with noise accounting for only 0.05% chance of this large *F*-value, indicating it is significant. Besides, *p*-value < 0.05 indicates the model term is significant, while a *p*-value > 0.05 suggests the model term is insignificant. In this case, term *C*, *BC*, C^2 are significant model terms. This implies that internal phase concentration plays a significant role in the IBP extraction. Jiao et al. reported that internal phase can stabilise the emulsion and minimise the breakage rate which enhance the extraction efficiency.[22] The "Lack of Fit *F*-value" of 175.81 suggests that it is significant with only 0.01% chance that "Lack of Fit *F*-value" this large due to noise. The predicted R^2 of 0.3376 is not in reasonable agreement with the adjusted R^2 of 0.9047. This may indicate a large block effect or a possible problem with model and/or data. Things to consider are model reduction, response transformation, outliers, etc.[23] "Adequate Precision" measures the signal to noise ratio. A ratio greater than 4 is desirable. Here the ratio of 12.436 indicates an adequate signal.

3.3 Interaction of Parameters on Extraction Efficiency

3.3.1 Carrier and surfactant concentration

Contour plot and 3D response surface curves for extraction of IBP are plotted to present the interaction of the independent parameters and to determine the optimum value for the investigated parameters to achieve high extraction efficiency (responses). Figure 1 depicts the contour plot and responses surface for interaction of carrier Aliquat 336 and surfactant Span 80 towards extraction efficiency of IBP.

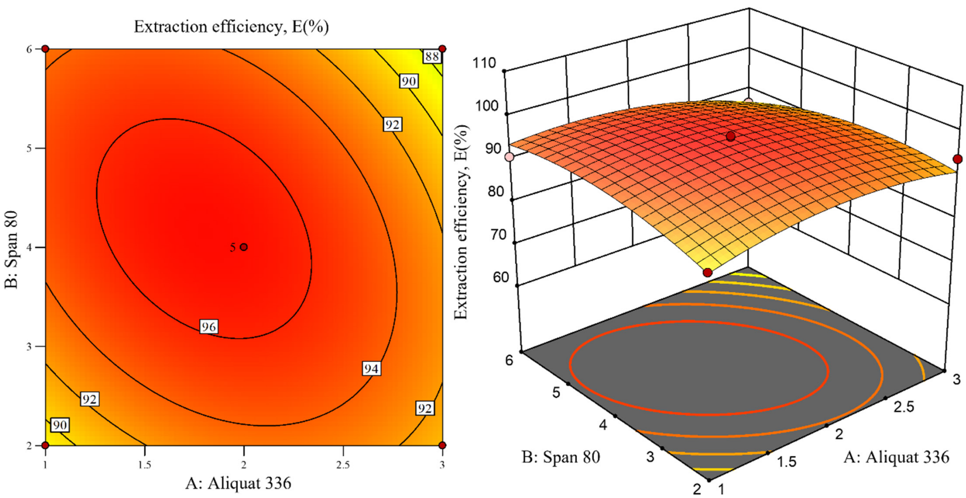

Figure 1: Contour and 3D response surface plot for extraction efficiency of IBP at various A: Aliquat 336 and B: Span 80 level.

In Figure 1, the circular contour indicates that the interaction between Aliquat 336 and Span 80 is insignificant and that the optimum values for these parameters cannot be determined. The interactive effect of the Aliquat 336 concentration and Span 80 concentration on the extraction efficiency of IBP depicts a response surface with a local maximum of IBP extraction at 2 wt% of Aliquat 336 and 4 wt% of Span 80. The extraction efficiency increased at Aliquat 336 concentration from 1 wt% to 2 wt% and decreased significantly from 2 wt% to 3 wt%. Beyond 2 wt%, emulsion viscosity increased due to the increase in of mass transfer resistance of the IBP towards the internal phase.[5] Enhancing concentration of Span 80 greater than 4 wt% lead to emulsion swelling due to the increase in the hydration capacity.[5] According to Table 3, the *F*-value of 15 with the chance of 24% of this high due to noise implies the term *AB* is insignificant.

3.3.2 Carrier and stripping agent concentration

The interactive effect of carrier and stripping agent concentration on IBP extraction is investigated over a parametric range of 0.05 M–0.15 M Na_2CO_3 and 1 wt%–3 wt% Aliquat 336. Figure 2 shows the contour plot and responses surface for interaction of carrier Aliquat 336 and stripping agent Na_2CO_3 towards extraction efficiency of IBP. The elliptical nature of the contours implies term *AC* is significant. The maximum extraction efficiency is obtained when Aliquat 336 and Na_2CO_3 at 2 wt% and 0.1 M, respectively. As the concentration of Na_2CO_3 exceeds 0.1 M, the extraction efficiency shows a downward trend. This is as a consequence of instability of emulsion caused by the increased in the concentration difference between the feed and internal phase thus led to membrane breakage.[22]

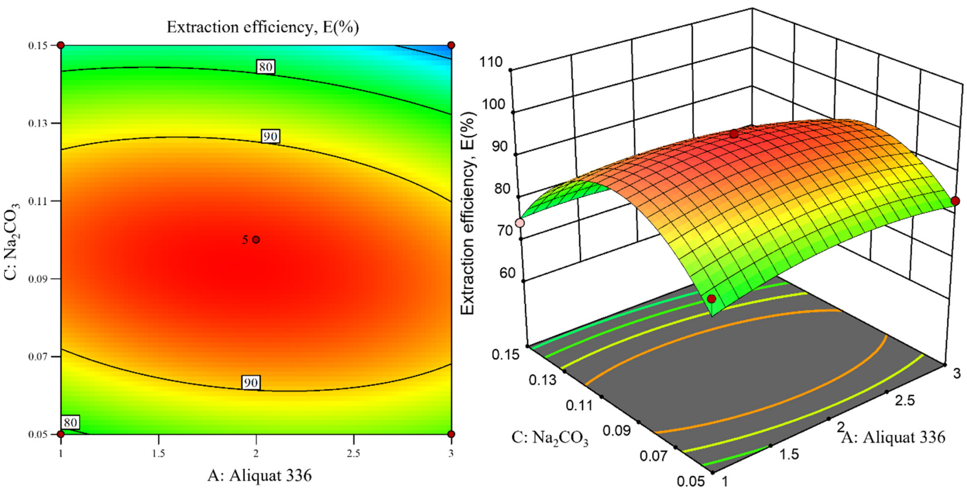

Figure 2: Contour and 3D response surface plot for extraction efficiency of IBP at range *A*: Aliquat 336 and *C*: Na_2CO_3.

3.3.3 Surfactant and stripping agent concentration

Surfactant and stripping agent concentration are factors that determine the extraction efficiency of IBP via ELM. Figure 3 depicts the interaction of *B*: Span 80 and *C*: Na_2CO_3 towards the extraction efficiency of IBP. The elliptical contour is the evident showing a significant interaction between the two investigated parameters. This is supported by the *F*-value of 17.43 having 0.4% chance due to the noise as shown in Table 3. The presence of Span 80 in the emulsion can increase the contact area between feed and internal phase.

The increased of Span 80 concentration beyond 4 wt% has slowed down the increasing extraction efficiency due to the formation of large globules.[24] Therefore, the maximum extraction removal is found at 4 wt% of Span 80 and 0.1 M of Na_2CO_3.

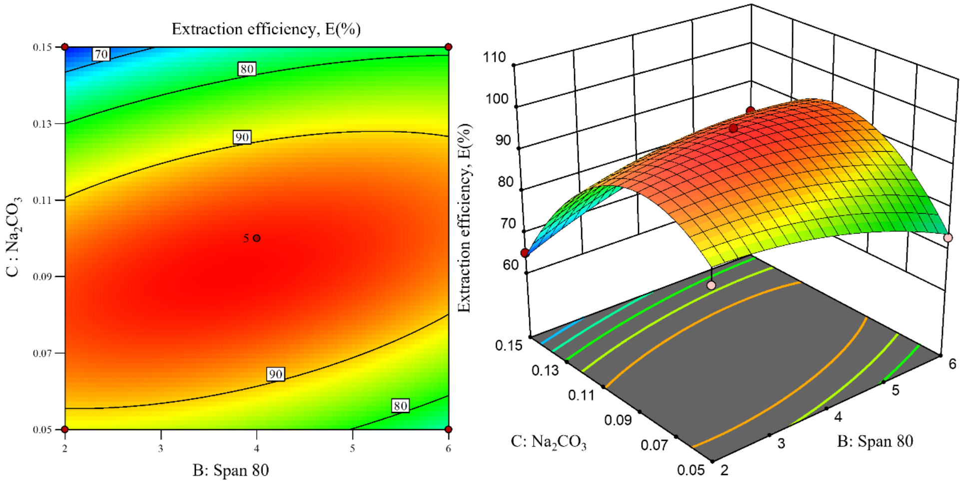

Figure 3: Contour and 3D response surface plot for extraction efficiency of IBP at range *B*: Span 80 and *C*: Na_2CO_3.

3.4 Validation of Test Results

The extraction efficiency of generated model is tested using optimisation program in the Design Expert tool. Figure 4 shows the ramp graph for the desirability function for the optimisation. Desirability close to 1 indicates that predicted main parameter values and extraction efficiency are highly fitted and suitable for experiments. The maximum extraction efficiency of IBP was found to be at *A* of 2 wt%, *B* of 4 wt% and *C* of 0.1 M. Under the optimal condition, the maximum predicted efficiency was 96.78%. Experimental extraction efficiency was found at 97.23%. Thus, relative error between experimental and BBD is about 0.46%. Hence, BBD is sufficient for the experimental modelling for IBP removal using ELM.

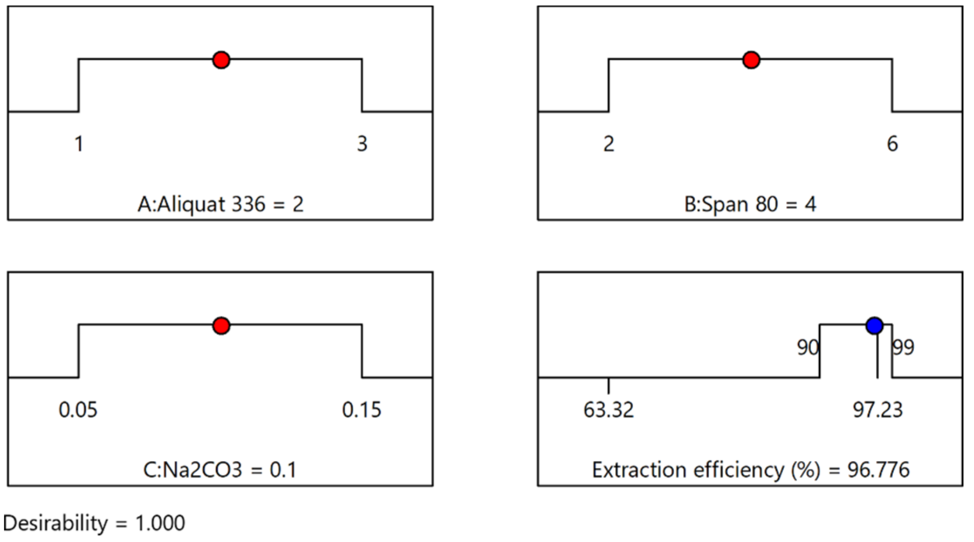

Figure 4: Ramp function graph of desirability of optimisation.

4. CONCLUSION

In conclusion, through BBD, the investigation was conducted to optimise the main parameters in ELM and to study the interactive effect between each parameter. It was found quadratic regression model is significant to study the interaction between main parameters. The most significant parameter was between Span 80 and Na_2CO_3 with a *p*-value of 0.4%. The optimum conditions for IBP extraction were found at 2 wt% of Aliquat 336, 4 wt% of Span 80 and 0.1 M of Na_2CO_3. Thus, this optimisation and statistical analysis can be used to predict IBP extraction efficiency in real-world applications for a variety of experimental environments.

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