OPTIMIZATION OF CURCUMIN ENCAPSULATION FORMULA WITH CHITOSAN AND ALGINATE USING SIMPLEX LATTICE DESIGN AND ITS EFFECT ON ANTIOXIDANT ACTIVITY

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Abstract

Curcumin is known to enhance the performance of antioxidant serums, such as superoxide dismutase (SOD). However, curcumin is prone to degradation when exposed to sunlight, necessitating the use of encapsulation technology to protect it from chemical degradation and improve its dispersibility. Biopolymers like chitosan and alginate are commonly used as encapsulation materials. This study aimed to determine the ideal concentrations of chitosan and alginate for curcumin encapsulation and evaluate its antioxidant activity. The optimal formulation was identified using Design Expert software version 13 with a Simplex Lattice Design. Encapsulation was carried out through the ionic gelation method, and the curcumin encapsulates were evaluated for encapsulation efficiency, particle size, zeta potential, and antioxidant activity. The optimal formulation was found to be 1.35% chitosan and 2.145% alginate, achieving an encapsulation efficiency of 71.85%, a particle size of 551.1 nm, a zeta potential of -46 mV, and strong antioxidant activity with an IC50 value of 36.32 ppm. In conclusion, the Simplex Lattice Design method successfully optimized the formulation. Chitosan increased particle size, while alginate enhanced encapsulation efficiency. The antioxidant activity was minimally affected by encapsulation, as most curcumin was retained in the droplets. The zeta potential value confirmed the stability of the encapsulate.

***Keywords**: alginate, antioxidant activity, chitosan, curcumin, encapsulation*

Introduction

Curcumin is a compound derived from turmeric and has been used as an herbal medicine because of its therapeutic benefits. Curcumin (77%), demethoxycurcumin (17%), and bisdemethoxycurcumin (3%) are curcuminoid polyphenols found in turmeric (Kocaadam and Şanlier, 2017). Curcumin is the most biologically active among the other two compounds, thus becoming a focal point in developing pharmaceutical products, supplements, and food. Curcumin can enhance the performance of antioxidant serums like superoxide dismutase (SOD). Additionally, it can neutralize various types of free radicals, including ROS and RNS, through diverse mechanisms. These mechanisms include modulation of enzyme activity, such as GSH, catalase, and SOD, which play a crucial role in counteracting free radicals, as well as inhibition of enzymes that produce ROS, such as lipoxygenase, cyclooxygenase, and xanthine hydrogenase (Hewlings and Kalman, 2017).

Curcumin is associated with benefits for skin health due to its antioxidant and anti-inflammatory properties. In the research (Moon-ai *et al.*, 2012), turmeric exhibited SOD activity with a low IC_{50}

value for both crude extracts, specifically 0.0179 µg/mL. Curcumin is a potential therapeutic agent, but it exhibits poor stability both in storage and under physiological conditions in the body. It is sensitive to sunlight exposure and can degrade into ferulic acid, ferulic aldehyde, vanillin, and vanillic acid (Kotha and Luthria, 2019). Additionally, curcumin has low water solubility. Given these weaknesses, effective technology is required to overcome these challenges. One approach is to utilize encapsulation technology to protect curcumin from chemical degradation and enhance its water dispersibility (Zheng and McClements, 2020)

Encapsulation materials can be either biopolymers or synthetic. Biopolymer materials offer several advantages over synthetic ones, including being non-toxic, non-reactive in human skin tissue, and capable of being metabolized by the body. In the study of 1% curcumin encapsulation using potato starch (Pires *et al.*, 2022) it has the greatest ability to inhibit ABTS radicals (45% inhibition). Research (Meng *et al.*, 2021) on zein-encapsulated curcumin and carboxymethyl dextrin also showed an ABTS radical inhibition value of 73.3%. Encapsulation of curcumin using whey protein causes an increase in the DPPH radical inhibition value compared to free curcumin and causes an increase in the oxidation stability of curcumin from 10% to 70% (Solghi *et al.*, 2020). Research conducted (Kumar *et al.*, 2015) namely the encapsulation of flavanone naringenin by the ionic gelation method using chitosan and TPP, showed significant antioxidant activity.

The chitosan amino group has a cationic character, so it can cause strong electrostatic interactions between chitosan and anionic drugs. Chitosan has hydrophilic characteristics, so it can form a gel when in contact with anions. Ionic gelation is one method for the encapsulation process, based on the electrostatic interaction between the positively charged amino group (-NH_2) on chitosan and the negatively charged polyanion group. This interaction facilitates the encapsulation process. Sodium tripolyphosphate (Na-TPP) is a commonly used polyanion because it is non-toxic, affordable, stable, and possesses more negative charges than other polyanions, which enhances the strength of the interaction (Edityaningrum *et al.*, 2022).

In the research (Akolade *et al.*, 2018) utilizing the ionic gelation method, the addition of 3% alginate to the 0.25% chitosan formula impacted encapsulation efficiency, with lower chitosan concentrations and higher alginate concentrations resulting in increased encapsulation efficiency. Determining the optimal proportion between chitosan and alginate requires optimization using Design Expert version 13. One method within Design Expert version 13 is simplex lattice design, which can provide optimal formulas based on response parameter data. The Simplex Lattice Design (SLD) optimization method seeks to ascertain the proper material concentration, producing a formula with ideal physical characteristics and suitable reactions. Formulas with different material combinations can be optimized using the SLD approach, resulting in formulas with the required physical properties. Because it eliminates the need for trial and error in figuring out the formula, this method is said to be quick and useful (Purwanto *et al.*, 2024)

Based on the description above, this research aimed to determine the optimal formula of chitosan and alginate in the curcumin encapsulation process and subsequently test their antioxidant activity.

Research Methods

Provide thorough details on the materials, instruments, and procedures to allow accurate reproduction of the work.

Describe only essential techniques, including citations for referenced methods, and clearly note any modifications. Specify the equipment by trademark and model, and list materials along with the supplier's name and country of origin.

Materials

Curcumin (Gansu Yasheng Hiosbon Food Group, China), chitosan (Chimultiguna Bio Chitosan, Indonesia), alginate (Sigma Aldrich, USA), *diphenylpicrylhydrazyl* (DPPH) (Sigma Aldrich, U.S.A), tripolyphosphate sodium (Xilong scientific, China), ethanol 96%, methanol (Merck, Germany), aquadest.

Instrumentation

Particle Size Analyzer (Malvern Masterzier, United Kingdom), UV-Vis spectrophotometer (Shimadzu UV-1800, Japan), magnetic stirrer (Thermo Scientific, USA), centrifuge (PLC Series, Gemy, Taiwan).

Procedure

1) Design of curcumin encapsulation formula using the Simplex Lattice Design method

The chitosan and alginate formulas were designed using the Simplex Lattice Design method using Design Expert version 13.

Table 1. Chitosan-alginate design for curcumin encapsulation using Simplex Lattice Design

Formula	Chitosan (%)	Alginate (%)
Run 1	1.21	2.28
Run 2	0.5	3
Run 3	0.63	2.87
Run 4	0.78	2.72
Run 5	1.35	2.14
Run 6	0.5	3
Run 7	1.10	2.39
Run 8	1.22	2.28
Run 9	1.5	2
Run 10	1.5	2
Run 11	0.90	2.6
Run 12	1.01	2.49
Run 13	0.78	2.72
Run 14	0.78	2.72

2) Preparation of chitosan and alginate solution

Chitosan solution was prepared by dissolving chitosan of various concentrations in a 1% acetic acid solution and then adjusting the volume to 100 ml with distilled water. Alginate solution is made by dissolving sodium alginate at each concentration, adding it to 100 mL of distilled water, and then homogenizing it. (Yousefi *et al.*, 2020).

3) Curcumin encapsulation process with chitosan and alginate using the ionic gelation method

Chitosan was dissolved in 100 ml of 1% acetic acid, and 1.5% TPP was dissolved in distilled water. Then, 25 mg of curcumin was dissolved in 100 ml of ethanol and combined with the chitosan solution. The chitosan-TPP complex was created by gradually adding the TPP solution to the chitosan solution drop by drop while stirring at 700 rpm with a magnetic stirrer. Once the complex was formed, it was mixed with 100 ml of a

previously prepared alginate solution (Akolade *et al.*, 2018).

4) Characterization of curcumin encapsulates

Characterization parameters for curcumin encapsulates, including particle size, zeta potential, and encapsulation efficiency. The curcumin encapsulation results were characterized by measuring particle size and zeta potential using a particle size analyzer (PSA), with all measurements conducted in triplicate (Lee *et al.*, 2019). The determination of encapsulation efficiency involved dissolving 5 mL of curcumin encapsulated in 5 mL of ethanol, followed by centrifugation at 350 rpm for 40 minutes until two layers formed in a test tube. Encapsulation efficiency was determined by measuring the concentration of unencapsulated curcumin in the supernatant. The unencapsulated curcumin was then analyzed with a UV-Vis spectrophotometer at a wavelength of 426 nm. (Hudiyanti *et al.*, 2022). This experiment was repeated three times, and the absorption efficiency was calculated using the following formula in Equation (1).

$$\text{Encapsulation Efficiency (\%)} = \frac{\text{Co-Ct}}{\text{Co}} \times 100\% \quad (1)$$

Description:
Co = The concentration of encapsulated curcumin
Ct = The concentration of unencapsulated curcumin

5) Antioxidant activity

Preparation of DPPH stock solution is as much as 15.8 mg of DPPH powder dissolved in 100 ml methanol, obtaining a DPPH concentration of 0.4 mM. Then the maximum wavelength of DPPH was determined by taking 1 ml of DPPH solution (0.4 mM) and adding 5 ml of methanol solvent, and then measuring the absorbance using a UV-Vis spectrophotometer with a wavelength of 450–550 nm (Andriani and Murtisiwi, 2020). Antioxidant activity measurements were carried out on curcumin before and after encapsulation by chitosan and alginate. Curcumin before and after encapsulation was made in a concentration series of 10, 15, 20, 25, 30, and 35 ppm. Each sample concentration was taken in 1 ml and then added with 3 ml of a 0.4 mM DPPH solution. The DPPH radical-scavenging activity was calculated using the following Equation 2.

The blank indicates the absorbance of the control (DPPH), while the sample absorbance represents the test compound. The concentration needed to achieve 50% inhibition (IC_{50}) is determined by plotting the percentage of inhibition against the sample concentration on a graph (So¨kmen and Khan, 2016).

$$\text{DPPH Scavenging Effect (\%)} = \frac{\text{A blank-A sample}}{\text{A blank}} \times 100\% \quad (2)$$

Description:
A blank : Control absorbance
A sample : Sample absorbance

6) Determination of the Optimum Formula

The results of the characterization and antioxidant activity tests of curcumin encapsulation were analyzed using Design Expert version 13. The analysis aimed to determine the optimal levels of alginate and chitosan that would provide the best encapsulation formulas, considering parameters such as encapsulation efficiency, particle size, zeta potential, and antioxidant activity.

Results and Discussion

Testing of curcumin encapsulation characteristics includes particle size, zeta potential, and encapsulation efficiency. Particle size plays an important role in diffusion, permeability, and controlled release processes. In general, encapsulated particles are classified into nanocapsules (smaller than 200 nm), microcapsules (200–5000 nm), and macrocapsules (larger than 5000 nm) (Jafari, 2017). The zeta potential value is a parameter that measures the stability of the charge or repulsion between emulsifier particles (Fırtın *et al.*, 2020). The stability of the surface charge (zeta potential) determines whether the charge on the droplet surface is anionic, cationic, or nonionic. Zeta potential is considered stable if it is greater than +30 mV or less than -30 mV (Dipahayu and Kusumo, 2021). Encapsulation efficiency is a parameter to evaluate the success of a drug delivery system. This value represents the percentage of material successfully encapsulated into the drug carrier after encapsulation, providing protection, absorption, delivery within the body, and controlled release (Hudiyanti *et al.*, 2022).

Optimization of chitosan and alginate formula with simplex lattice design

The relationship between the independent variables (chitosan and alginate) and the dependent variables (particle size, encapsulation efficiency, zeta potential, and antioxidant activity) can be described using a linear model. The correspondence between the data distribution and this model can be evaluated using an ANOVA test. This test assesses the significance of the model, the lack of fit, and the coefficients of determination (predicted R-squared and adjusted R-squared) using Design Expert version 13, as shown in Table 2.

Table 2. ANOVA results for the experimental design of particle size, zeta potential, encapsulation efficiency, and antioxidant activity of encapsulated curcumin.

Parameter	Model (p<0.05)	Lack of Fit (p>0.05)	Adjusted R^2	Predicted R^2	Adeq Precision (>4)
Particle size	*Quartic* (p = 0.03)	0.3325	0.9636	0.9156	25.692
Zeta potential	*Cubic* (p = 0.0079)	0.0642	0.5821	0.4034	7.5467
Encapsulation efficiency	*Quartic* (p = 0.0001)	0.0638	0.9316	0.8885	18.49
Antioxidant activity	*Quartic* (p = 0.0372)	0.05746	0.4863	0.2599	6.171

ANOVA Design Expert version 13 analysis of all curcumin encapsulate responses obtained significant response model results ($p < 0.05$), indicating that the model can describe the data distribution. The software-generated model fits the response if the significance value (p) > 0.05 shows a lack of fit on the insignificant response. When choosing the right model, the response's adjusted R^2 and anticipated R^2 values serve as a guide. The response model with the greatest

adjusted R^2 and anticipated R^2 values was selected. A lack of fit that is not statistically significant suggests that the model is adequate and fits the answer. The degree of variation surrounding the average model response is shown by the R^2 value. The R^2 number needs to be near 1. The range of expected answers in relation to the inaccuracy is a measure of adequate precision. It is anticipated that adequate precision would be higher than 4 (Akbar *et al.*, 2022).

Particle size analysis with simplex lattice design

The results of testing the particle size of curcumin cream encapsulated with chitosan and alginate using a particle size analyzer showed sizes ranging from 331.7 to 1100 nm. The results were then analyzed using Design Expert version 13. Analysis of the particle size response to chitosan and alginate produced the linear Equation 3.

$$Y = 1028.55A + 368.225B + 1217.3AB \quad (3)$$

Description:
Y = Particle size (micrometer)
A = Chitosan (%)
B = Alginate (%)

As shown in Figure 1, the graph of the particle size response model indicates that higher chitosan concentrations tend to increase particle size. The increase in chitosan concentration has an impact on the average particle size because the number of chitosan molecules cross-linked via TPP ions increases, forming larger particles. This increase is caused by intermolecular hydrogen bonds and electrostatic repulsion (Benamer Oudih *et al.*, 2023). Research conducted (Dwitarani *et al.*, 2021) in the manufacture of nano herbals using chitosan and Na TPP by the ionic gelation method also shows that the higher the concentration of chitosan, the larger thein particle size.

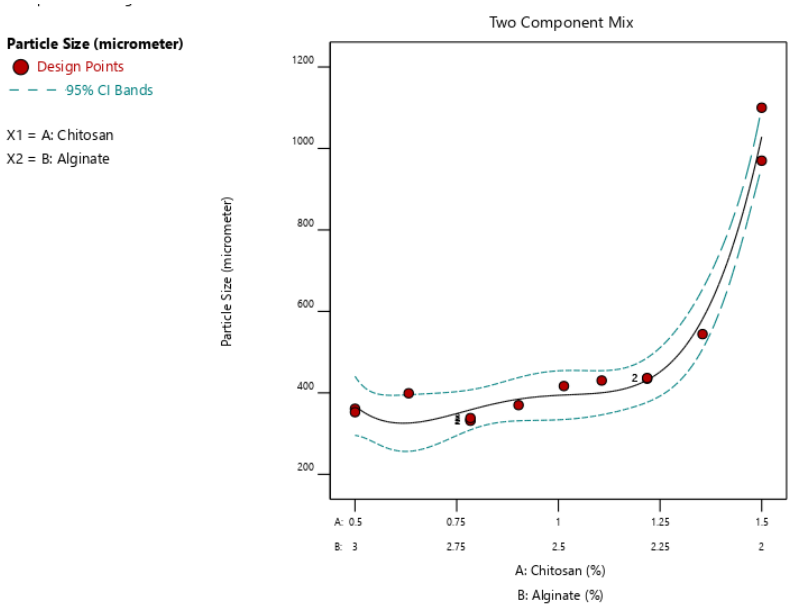

Figure 1. The particle size response model

Potential zeta analysis with simplex lattice design

Potential zeta testing on encapsulated curcumin obtained results of -36.7 to -57.1 mV and met the requirements for a zeta potential value of less than -30 mV. The results of the potential zeta response analysis produce the line Equation 4.

Based on the graph of the zeta potential response model depicted by the Design Expert version 13 in Figure 2, a concentration optimum of 1.5% chitosan and 2% alginate produces the highest zeta potential value. The charge on the surface of chitosan particles that have the NH_2 functional group or alginate, which contains the COOH functional group, influences the zeta potential value (Prasetyo *et al.*, 2018). The concentration of alginate, which is anionic, is higher than that of chitosan, which is cationic, causing the surface of the curcumin encapsulate to be dominated by anionic compounds, resulting in a negatively charged zeta potential (Amin and Boateng, 2022).

$$Y = -39.0417A - 54.1114B - 54.902AB \ (A-B) \quad (4)$$

Description:
Y = Potential Zeta (mV)
A = Chitosan (%)
B = Alginate (%)

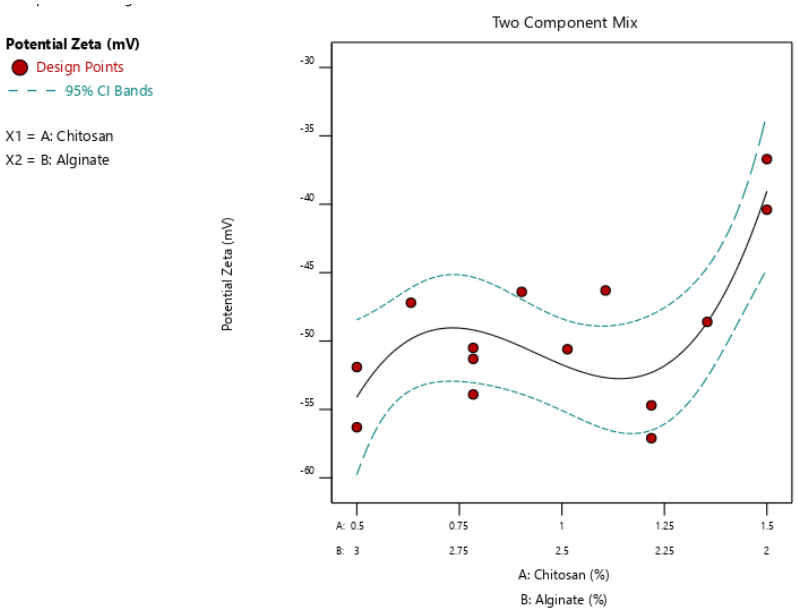

Figure 2. The zeta potential response model

Encapsulation efficiency analysis with simplex lattice design

Encapsulation efficiency depends on the type of drug and its interaction with the polymer. Chitosan is a weak polyelectrolyte with a pKa of around 6.5. The higher the alginate concentration, the viscosity of the solution will increase, causing bioactive compounds to be trapped in large quantities (Machado *et al.*, 2022). In Figure 3, the graph of the encapsulation efficiency response model, as explained by Design Expert version 13, shows that higher alginate concentrations lead to greater encapsulation efficiency. Analysis of encapsulation efficiency yielded a response with the linear Equation 5.

$$Y = 66.2371A + 73.9582B + 16.8212AB \quad (5)$$

Description:
Y = Encapsulation Efficiency (%)
A = Chitosan (%)
B = Alginate (%)

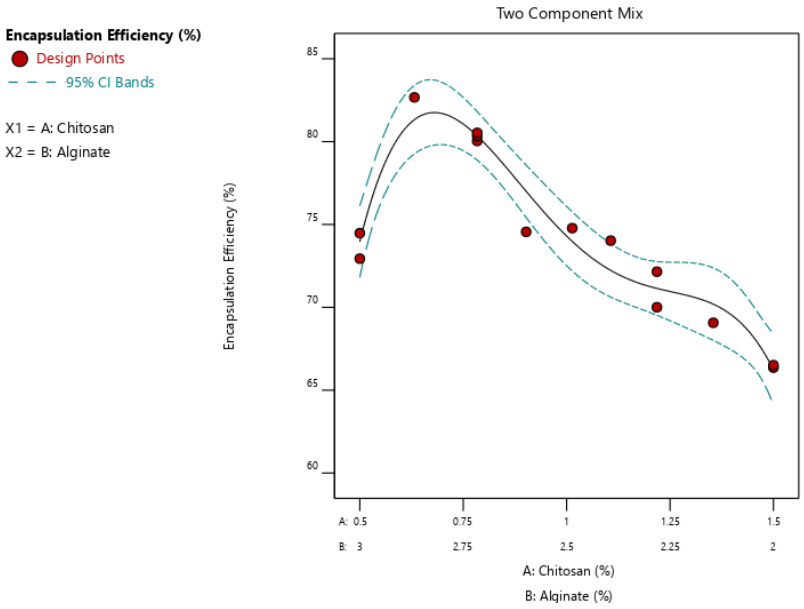

Figure 3. The encapsulation efficiency response model

The interaction between cationic and anionic biopolymers will result in the formation of polyelectrolyte complexes, thereby increasing encapsulation efficiency(Akolade *et al.*, 2018) . In a study conducted by (Jayanudin *et al.*, 2017), the combination of chitosan and alginate on ginger oleoresin produced a higher encapsulation efficiency value than using only chitosan, which was 85.17%. The combination of chitosan and alginate causes polymer crosslinking interactions so that the microcapsule walls are stronger so that the main ingredients can be well coated. In addition, the addition of a Na TPP crosslinking agent can strengthen the network structure in the system. Na TPP interacts with chitosan, causing the chitosan polymer chains to become denser. The presence of alginate further strengthens the density of the polymer chains. The combination of chitosan and alginate supplemented with Na TPP results in an ionic reaction where STPP polyanions and alginate react with chitosan polycations, forming a sturdier matrix (Jayanudin *et al.*, 2017).

Antioxidant activity analysis with simplex lattice design

Curcumin, a polyphenol with antioxidant properties, has been shown to enhance the activity of serum antioxidants like superoxide dismutase (SOD). (Hewlings and Kalman, 2017). SOD protects the skin from damage caused by reactive oxygen species (ROS), which are induced by UV exposure (Liu *et al.*, 2018). The evaluation of antioxidant activity was carried out in vitro using the DPPH method. The DPPH approach is able to provide an overview of how effective an antioxidant is at reducing free radicals. The DPPH test parameter used is the IC_{50} value, namely the antioxidant concentration (µg/mL) required to inhibit DPPH free radical activity by 50%. Determining the maximum wavelength is the first step in assessing antioxidant activity because equipment and condition

differences can impact the results. The maximum wavelength, as determined by (J.Rohmah, 2020), is between 514 and 519 nm, with a value of 516 nm. A wavelength of 515 nm, on the other hand, is still within the maximal wavelength range for radical scavenging activity according to the measurement results of this curcumin study. The analysis of the antioxidant activity response yielded the linear Equation 6.

$$Y = 35.754AB\ (A-B)^2 \quad (6)$$

Description:
Y = Antioxidant activity (ppm)
A = Chitosan (%)
B = Alginate (%)

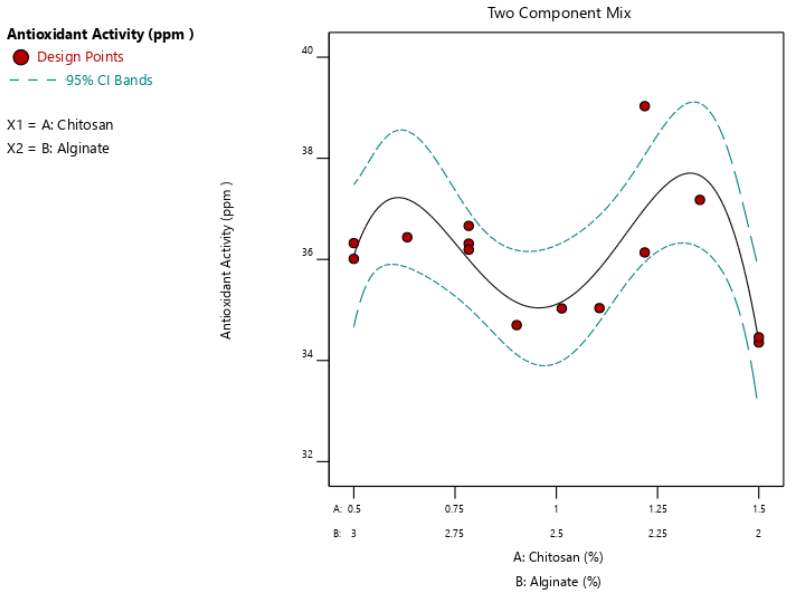

Figure 4. The antioxidant activity response model

From the graph of the antioxidant activity response model depicted by Design Expert version 13 in Figure 4, a concentration of 1.5% chitosan and 2% alginate produces the lowest IC_{50} value, indicating the highest antioxidant activity. The research results showed that the IC_{50} value of curcumin before and after the encapsulation process was <50 ppm, which indicates a very strong antioxidant. The concentration of chitosan and alginate in the encapsulation process did not affect the antioxidant activity of curcumin because the IC_{50} was not significantly different. Curcumin functions as an antioxidant by providing one hydrogen atom to the DPPH radical molecule, which tends to be unstable. This causes the DPPH radical to become stable, and the absorbance value of the test solution tends to decrease as the concentration of the test solution used increases. The recorded absorbance values reflect the remaining DPPH radicals, which are not captured by antioxidant compounds (Hidayat *et al.*, 2018).

The IC50 result of curcumin before encapsulation was 33,48 ppm while after encapsulation with various concentrations of chitosan and alginate, it was between 34,36 - and 39,03 ppm. These results showed no significant difference in the antioxidant activity of curcumin encapsulated in chitosan and alginate. The slight decrease in the antioxidant capacity

of encapsulated curcumin could be due to the good entrapment of curcumin in the encapsulated droplets, and a decrease in antioxidant activity was also reported as a result of encapsulation in complex systems compared to curcumin in ethanol solution (Scomoroscenco *et al.*, 2022). Research conducted by Ang *et al.*, 2019 also showed no significant difference between unencapsulated curcumin and curcumin encapsulated with chitosan.

Determination of optimum chitosan and alginate formula

The test results for particle size, zeta potential, encapsulation efficiency, and antioxidant activity were optimized using Design Expert version 13. This resulted in an optimal formula of 1.35% chitosan and 2.145% alginate with a desirability value of 1. A desirability value near one indicates that the response values are close to the target(Akbar *et al.*, 2022). The optimum formula was then encapsulated with curcumin and tested for each parameter. The results of testing the characteristics and antioxidant activity of the optimum concentrations of chitosan and alginate are shown in Table 3. The analysis using Design Expert version 13 predicted the response to the characteristics of the optimal encapsulation formulation. These predictions were then compared with the results of testing the optimal formula using IBM® SPSS® Statistics 25. The statistical analysis method applied was the one-sample t-test, as all data exhibited a normal distribution. The one-sample t-test results reveal no significant differences (sig > 0.05) between the experimental response values for encapsulation efficiency, particle size, zeta potential, and antioxidant activity and the predicted values from Design Expert version 13. Thus, it can be concluded that the Simplex Lattice Design method accurately predicts the encapsulation efficiency, particle size, zeta potential, and antioxidant activity of curcumin encapsulated with a combination of chitosan and alginate.

Table 3. Results of testing the characteristics and antioxidant activity of the optimum concentrations of chitosan and alginate

Response	Predicted Mean	Observed
Particle size	581.295	551.1
Zeta potential	-48.622	-46.4
Encapsulation efficiency	70.193	71.848
Antioxidant activity	37.660	36.32

Conclusions

The research concludes that the determination of the optimal formula using the simplex lattice design method resulted in an optimal chitosan concentration of 1.35%, which can increase the particle size (551.1 nm), and an alginate concentration of 2.145%, which can improve the encapsulation efficiency (71.828%). The antioxidant activity before and after encapsulation did not show a significant difference, indicating that it did not have a major impact on the encapsulation process because curcumin was largely absorbed in the droplet and the IC50 value < 50 ppm, which means it has very strong activity. The zeta potential value indicating stability meets the requirement of -46.4 mV, meaning the encapsulation of curcumin with chitosan and alginate is stable.

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