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Optimization of the ultrasound-assisted synthesis of lutein disuccinate using uniform design

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ABSTRACT

The ultrasound-assisted synthesis of lutein disuccinate from all-trans lutein (AL) and succinic anhydride (SA) was investigated in this study. Triethylamine was used as the catalyst. Based on the single-factor experiments, a 7-level-3-factor uniform design and response surface analysis were further employed to evaluate the effects of the selected variables including molar ratio of SA/AL, reaction time and ultrasonic power on the yield of lutein disuccinate. The results indicated that the data were adequately fitted into a second-order polynomial model; the molar ratio of SA/AL significantly affected the synthesis of lutein disuccinate, whereas reaction time and ultrasonic power did not. Based on ridge max analysis, the optimum condition for lutein disuccinate synthesis was predicted to be the molar ratio of SA/AL 265.3:1, ultrasonic power 300 W and reaction time 131.6 min with the lutein disuccinate yield of 80.53 ± 0.18%, which give a 43.8% increase compared with the traditional method, and also significantly shorten the reaction time.

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1. Introduction

Many studies have demonstrated the utility of lutein-based supplementation for the clinical improvement of vision, reduction of ultraviolet (UV)-based inflammation, and potentially the inhibition and/or amelioration of age-related macular degeneration (AMD) [1,2]. Although xanthophylls of the C40 series such as lutein, zeaxanthin, and astaxanthin extracted from plant materials have been approved for use as aqueous-phase singlet oxygen quenchers, direct radical scavengers, and lipid-peroxidation chain-breakers, and complicates parenteral delivery of these compounds, their low aqueous solubility and low stability in the native state have limited their uses in the food industry [3]. One way to increase the solubility of lutein in water-based formulas and dispersions is to esterify the compounds with aliphatic acids.

In the recent years, some C40-xanthophylls have been successfully modified. Hawaii Biotech, Inc. (HBI) synthesized a novel carotenoid derivative, the disodium disuccinate derivative of synthetic astaxanthin [3]. This novel derivative exhibits good water dispersibility. Nadolski had reported that two novel lutein derivatives were synthesized by esterification with inorganic phosphate and succinic acid, respectively [4]. In general, their preparation by purely chemical means requires vigorous conditions, high temperatures with incomplete conversions (below 60%), very long stirring times (up to 18 h) can lead to the formation of colored by-products and to the destruction of reaction products.

Nowadays, ultrasound-assisted synthesis as an effective technique is widely used in chemical reactions, which exhibits many advantages including higher yield, shorter reaction time and milder reaction condition when compared with conventional methods [5–9]. Ultrasound irradiation is well known to accelerate chemical reactions [10]. This is due to the phenomenon of acoustic cavitation, that is, the formation, growth and collapse of micrometrical bubbles, formed by the propagation of a pressure wave through a liquid. The collapses are quasiadiabatic processes, resulting in the generation of high temperatures and pressures in the nanosecond time scale, accompanied by sonoluminescence and mechanical effects. These effects can be used to accelerate chemical reactions, reducing the reaction time and optimizing the benefit-cost relation. Up to our best knowledge, usage of ultrasound-assisted synthesis has not been previously reported in lutein derivatives.

The experimental technique of uniform design is a new method established together by Fang et al. [11]. It applies the experiments with many factors and many levels and is based on orthogonal test. Uniform design allows the largest possible amount of levels for each factor, and the number of levels can be equal to the number





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of experiment runs, which has been successfully used for developing, improving and optimizing processes [12,13]. In general, Uniform design is preferred since it reduces the number of experiments significantly to evaluate multiple parameters and their interactions. Therefore, it is less laborious and time-consuming than other approaches required to optimize a process.

In order to study the optimal conditions to obtain the best possible yield in the succinic anhydride esterification of lutein under ultrasonic conditions, this work aims to optimize this reaction using a uniform design.

2. Materials and methods

2.1. Materials

All-trans lute in (\sim 90.42%) was prepared from marigold flowers and purified in our laboratory.

Chemicals: Analytical grade triethylamine, methylene chloride and acetic acid were all from Sinopharm Chemical Reagent Co., Ltd. HPLC-grade acetonitrile and methanol were purchased from TEDIA Company Inc. (Tedia Company, Inc., Fairfield, OH, USA). Deionized water was prepared with a Milli-Q system (Millipore, Bedford, MA, USA).

Apparatus: Desktop triple-frequency constant temperature numerical control ultrasonic cleaner from Kunshan Ultrasonic Instruments Co. Ltd. (KQ-300GVDV, Shanghai, China).

2.2. Synthetic procedure

The ultrasonic experiments were performed on a Kunshan KQ-300GVDV ultrasonic cleaner (Kunshan Ultrasonic Instruments Ltd. Co., China) with frequencies of 45 kHz, 80 kHz and 100 kHz. The flask mentioned below was located in the cleaning bath and the surface of reactants was slightly lower than the level of water in the cleaning bath. The temperature of the water bath was kept at 25 °C by the addition or removal of water. A reflux condenser was attached to the flask. The flask was sealed and purged with nitrogen to ensure an inert atmosphere for the reaction vessel.

Reaction scheme is depicted in Fig. 1. Appropriate quantities of all-trans lutein (AL), and succinic anhydride (SA) were added to a flame-dried flask in 10 mL of methylene chloride. After dissolution under manual agitation, the appropriate quantity of triethylamine was added. The mixture was submitted to ultrasonic irradiation under nitrogen atmosphere for 12 h, and thereafter, the solvent was evaporated. The residue was taken-up in 5 mL acetonitrile, the test solution was filtered through a 0.45 μ m microporous membrane, then for HPLC analysis. All operations were carried under dark conditions.

2.3. Determination of lutein disuccinate by analytical HPLC

YMC Carotenoid C30 column (4.6 mm \times 250 mm i.d., 5 μ m, YMC, Wilmington, NC) and HPLC (Agilent 1200 series, USA) was



Fig. 1. Synthesis of lutein disuccinate.

performed. Elution was carried out using solvent A and B (50:50, V/V) at a flow rate of 1.0 mL/min, and the eluents were examined by UV light at a wave-length of 450 nm. The binary mobile phase consisted of (A) acetonitrile:acetic acid (99.95:0.05, V/V) and (B) methanol:acetic acid (99.95:0.05, V/V).

2.4. MS and NMR confirmation

For MS, experiments were carried out on an Agilent 1290 Infinity LC/Agilent Technologies 6460 MS. The positive ion mode (APCI) was used to detect lutein and its esters, with total ion current (TIC) scanning range 50-1200 m/z, corona current 4 μ A, capillary voltage 4500 V and nitrogen as nebulizer gas (purity 99.9% and flow rate 4 L/min) and vaporizer temperature at 350 °C.

For NMR, 20 mg lutein disuccinate purified by preparative HPLC (Amersham Biosciences AKTA Purifier with Frac-900) was dissolved in CDCl₃. NMR experiments were acquired on an NMR spectrometer (BRUKER 300 MHz/52 mm, Milton, Ontario, Canada) at 298 K. The proton chemical shifts were referenced to the TMS signal at 0 ppm (25 °C).

2.5. Experimental design

At first, the effect of changing a single factor on the yield of lutein disuccinate was studied. Namely, we studied the variable condition of a factor when the others were invariable. Uniform design then was applied to determine the optimum condition of the ultrasound-assisted synthesis of lutein disuccinate. The investigated levels of each factor were selected depending on the above experiment results of the single factor. The combination affects of independent variables X_1 (molar ratio of SA/AL), X_2 (ultrasonic power, W) and X_3 (reaction time, min) at seven variation levels in the synthesis process, is shown in Table 1.

2.6. Statistical analysis

All the trials were performed in triplicate. For single-factor test, each data was average value of three parallel experiments. For uniform design and subsequent analysis, the software named as Data Processing System (DPS Version7.05, Refine Information Tech. Co., China) was used to generate statistical analysis and regression model. A total of seven combinations were chosen in random order according to DPS software configuration for three factors [14]. The coded and actual values are also shown in Table 1. The significance of each coefficient was determined using the Student's *t*-value and *p*-value, and the result is shown in Table 2.

3. Results and discussion

3.1. Single factor results

3.1.1. The effect of molar ratio of SA/AL on the yield of lutein disuccinate

This experiment adopted 50:1 M, 100:1 M, 150:1 M, 200:1 M, 250:1 M and 300:1 M ratio of succinic anhydride (SA) to all-trans lutein (AL) to study the effect of different molar ratio of SA/AL on lutein disuccinate yields in ultrasound-assisted synthesis. In these synthesis reactions, other experimental conditions were as follows: reaction temperature, 25 °C; ultrasonic power, 300 W; ultrasonic frequency, 45 kHz; catalyst concentration, 0.6% (percent by weight of AL).

The result shows that the yield of lutein disuccinate increased with elevating molar ratio of SA/AL, and the yield reached the highest when molar ratio of SA/AL increased to 250:1 (Fig. 2a). An enhancement in the concentration of succinic anhydride can

Table 1

Independent variables of the process and their corresponding levels.

Independent variables	Levels							
	1	2	3	4	5	6	7	
X_1 : molar ratio of SA/AL	200:1	220:1	240:1	260:1	280:1	300:1	320:1	
X ₂ : ultrasonic power (W)	120	150	180	210	240	270	300	
X_3 : reaction time (min)	25	50	75	100	125	150	175	

Table 2

Uniform design with the observed responses and predicted values.

No.	Varia	ble level	S	Y (%)		
	X_1	X_2	<i>X</i> ₃	Ye-Y	Experimental	Predicted
1	1	2	3	0.1030	29.91	29.0863
2	2	4	6	-0.0313	45.83	48.7317
3	3	6	2	-0.0606	57.43	55.8081
4	4	1	5	-0.0828	64.63	62.4838
5	5	3	1	-0.1159	24.05	23.5587
6	6	5	4	0.2610	52.21	56.5525
7	7	7	7	-0.0734	60.85	58.6889

displace the chemical equilibrium to products formation, resulting in higher conversions. On the other hand, excess succinic anhydride concentrations may reduce the reaction rate due to the inhibition effect. Similar results were observed by Zhen and Mo [15], where higher conversions (about 84%) in α -tocpheryl succinate were obtained at a molar ratio of 3:1. However, for a molar ratio value of succinic anhydride higher than three, reduction in production of α -tocpheryl succinate was observed.

3.1.2. The effect of ultrasonic power on the yield of lutein disuccinate

The effect of ultrasonic power on the lutein disuccinate yields had been studied in this work when different ultrasonic power (180 W, 210 W, 240 W, 270 W and 300 W) was set under the reaction conditions as follows: molar ratio of SA/AL, 250:1; reaction temperature 25 °C; ultrasonic frequency, 45 kHz; catalyst concentration, 0.6% (percent by weight of AL).

The result implied the yield of lutein disuccinate was always enhanced before the ultrasonic power 270 W, and then it reached the highest and was not changed when the ultrasonic power was increased (Fig. 2b). It appears that higher molar conversion was obtained with higher ultrasonic power. Xiao et al. [16] also demonstrated the ultrasound-accelerated synthesis of sugar esters. They suggested that the acceleration was likely due to an increase in collisions between the two substrates and the catalyst by ultrasound.



Fig. 2. Effect of the molar ratio of SA/AL (a), ultrasonic power (b), ultrasonic frequency (c) and catalyst concentration (d) on the reaction process curve.

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However, the reaction yields didn't show a continuous increase with ultrasonic power more than 270 W might due to the formation of large number of cavitation bubbles in the liquid [17,18]. The combination of these bubbles forming larger and more stable bubbles could create a barrier to the acoustic energy transmission throughout the reaction mixture leading to poor mixing effects between the two immiscible layers [19].

3.1.3. The effect of ultrasonic frequency on the yield of lutein disuccinate

This experiment adopted 45 kHz, 80 kHz, and 100 kHz ultrasound-assisted synthesis to investigate the effect of ultrasonic frequency on yields. Other experimental conditions were as follows: reaction temperature 25 °C; molar ratio of SA/AL, 250:1; ultrasonic power, 270 W; catalyst concentration, 0.6% (percent by weight of AL).

From Fig. 2c, it could be clearly seen that the lutein disuccinate yield gradually decreased with changed ultrasonic frequency, and the yield reached the highest (65.23%) when ultrasonic frequency was 45 kHz, and the reaction time was 2 h. Generally, higher frequencies are favorable from the point of view of energy efficiency of the sonochemical processes, at lower frequencies, the cavity grows to a larger size and the collapse is less violent [20]. Nevertheless, as the ultrasound frequency increases, the range of ambient radius for an active bubble becomes less wideness and the optimal ambient radius becomes smallest. Moreover, higher frequency cause the swelling time shorter, cavitation bubble has no time to collapse, so at the same operating intensity of irradiation, higher frequency will reduce cumulative effects of cavitation.

3.1.4. The effect of amounts of catalysts on the yield of lutein disuccinate

The effect of catalysts on the yields had been studied in this work when different amounts of catalysts (0.2%, 0.4%, 0.6%, 0.8% and 1.0%, percent by weight of AL) was set under the reaction conditions as follows: reaction temperature 25 °C; molar ratio of SA/AL, 250:1; ultrasonic power, 270 W; ultrasonic frequency, 45 kHz.

The effect of catalyst concentration on the rate of reaction has been shown in Fig. 2d. It can be seen from the figure that increase in rate of reaction is significant for increase in the catalyst concentration from 0.2% to 0.8%. But an increase in the catalyst concentration beyond 0.8% does not result in any further increase in rate of reaction and equilibrium conversion. Santos et al. [21] have reported similar effects of catalyst concentration on the ultrasound assisted esterification reactions.

3.2. Obtaining optimum synthesis condition

The uniform design method was used for more efficient optimization of the various operation variables in the ultrasound-assisted synthesis of lutein disuccinate. Based on the above results, three main factors were chosen, i.e., molar ratio of SA/AL, reaction time and ultrasonic power. A regression analysis was carried out to fit the mathematical model to the experimental data aiming at an optimal region for the studied. The following regression equation, which is an empirical relationship between the yield and the test variable in coded unit as given in Eq. (1), can describe the predicted model:

$$\begin{split} Y &= -498.16 + 4.21X_1 - 8.72 \times 10^{-3}X_1^2 + 2.30 \times 10^{-4}X_2^2 \\ &- 3.22 \times 10^{-3}X_3^2 + 3.22 \times 10^{-3}X_1 \times X_3 \end{split} \tag{1}$$

The multiple coefficient of determination (R^2) of the predicted model was 0.9796, suggesting a good fit, and the predicted model seemed to reasonably represent the observed values. Thus, the response was sufficiently explained by the model. The significance of

Table 3

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JODITICATION	nt	regression	coefficient	tor	the	weld	nt	lutein	disticcinate	٠
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Variables	Partial correlation	Computed <i>t</i> -value	Significance level <i>p</i> -value
$r(y, X_1)$	0.9776	4.6408	0.0434
$r(y, X_1^2)$	-0.9791	4.8181	0.0405
$r(y, X_2^2)$	0.9159	2.2823	0.1500
$r(y, X_3^2)$	-0.9601	3.4316	0.0754
$r(y, X_1X_3)$	0.9766	4.5426	0.0452

each coefficient was determined using the Student *t*-test and *p*-value in Table 3. The corresponding variables will be more significant if the absolute *t*-value becomes larger and the *p*-value becomes smaller [22]. It can be seen that the variable with the largest effect was the quadratic terms (X_1^2) , the linear terms of the molar ratio (X_1) , followed by interaction effects of the molar ratio and reaction time (X_1X_3) .

Then the prediction was obtained by DPS software. An optimum condition for the synthesis of lutein disuccinate which determined by ridge max analysis was found as follow: molar ratio of SA/AL with 265.3:1, ultrasonic power of 300 W, reaction time of 131.6 min. The adequacy of the predicted model (Eq. (1)) was examined by carrying out the lutein disuccinate synthesis experiment under the optimal condition afore-mentioned. The results showed lutein disuccinate yield of $79.78 \pm 1.18\%$ under the optimal condition. This observed value did not significantly differ from the predicted value of $80.53 \pm 0.42\%$. Thus, the model developed, as shown in Eq. (1), adequately predicts the yield in the lutein disuccinate synthesis reaction.

3.3. Comparison of ultrasound and conventional synthesis methods

The conventional synthesis method was carried out at ambient temperature by stirring magnetically at the highest possible speed of the stirrer to completely mix the two phases, other conditions were kept same with optimal ultrasound synthesis. Fig. 3 shows the effect of the ultrasound and conventional synthesis on lutein disuccinate formation. It has been observed that use of ultrasound enhances the limiting equilibrium conversion from about 56% in 12 h with conventional synthesis method to about 80% in 2 h of reaction time. Thus, the use of ultrasonic irradiations is in both enhancing the rate of reaction as well as in shifting the equilibrium and resulting in higher product yields. Ultrasound generated cavitation results in conditions of intense turbulence and micro-scale liquid circulation currents which help in uniform mixing at micro-level and hence in the elimination of the mass transfer

Fig. 3. Comparison between conventional and ultrasound esterification process curve.

Fig. 5. ¹H NMR spectrum.

resistances [23]. Moreover, because of the simultaneous nucleation and homogeneous heating, uniformly small particles can be synthesized.

3.4. MS and NMR confirmation

To confirm the structure of the target compound, a further purification was investigated by preparative HPLC; the purified compound was introduced by direct infusion and analyzed by APCI in the positive mode with m/z scan from 50 to 1200. The mass spectrum was shown in Fig. 4. Lutein disuccinate was identified based on the fragmentations at m/z 651.1 [M+H–118], 559.1 [M+H–118–92], 533.1 [M+H–118+H–118–H], due to the loss of one H₂O and one succinic anhydride, one H₂O and one succinic anhydride from the molecular ions at m/z 668.8.

Structure elucidation of isolated lutein disuccinate was further performed by NMR. Based on the ¹H NMR data (Fig. 5), the location of the hydrogen atom in the organic molecules, the relative number of hydrogen atoms in the mother nucleus skeleton and various functional groups, the spatial structure can be identified. ¹H NMR: $\delta 2\langle '' \rangle = 1.62, \ \delta 2 \langle '' \rangle = 1.62, \ \delta 3 = 5.11, \ \delta 4\langle '' \rangle = 2.37, \ \delta 4\langle ' \rangle = 2.37, \ \delta 7a = 6.14, \ \delta 8a = 6.36, \ \delta 10a = 6.14, \ \delta 11a = 6.64, \ \delta 14a = 6.27, \ \delta 15a = 6.64, \ \delta 16 = 1.09, \ \delta 17 = 1.12, \ \delta 18 = 1.74, \ \delta 19 = 1.98, \ \delta 20 = 2.11, \ \delta 22 = 2.7, \ \delta 23 = 2.69, \ \delta 24$ Exchangeable, $\ \delta 2'\langle '' \rangle = 1.62, \ \delta 2'\langle ' \rangle = 1.62, \ \delta 3' = 5.5, \ \delta 4' = 5.37, \ \delta 6'a$ Exchangeable, $\ \delta 15'a = 6.64, \ \delta 14'a = 6.27, \ \delta 12'a = 6.36, \ \delta 11'a = 6.64, \ \delta 10'a = 6.14, \ \delta 8'a = 6.14, \ \delta 7'a = 5.44, \ \delta 16' = 0.90,$

 $\delta 17' = 0.92$, $\delta 18' = 1.67$, $\delta 19' = 1.98$, $\delta 20' = 2.11$, $\delta 22' = 2.65$, $\delta 22' = 2.63$, $\delta 24$ Exchangeable.

4. Conclusions

After the experimental observations, it is possible conclude the ultrasound irradiation can improve the esterization of lutein, decreasing the time reaction and improving the yield of lutein disuccinate. The uniform design techniques helped us to understand the influence of the reagents in the yield, and the data provided by these findings are useful to optimize the synthesis of lutein disuccinate. Moreover, the obtained statistical model is considered well fitted and valid at the 95% confidence level. Through MS and NMR confirmation, lutein disuccinate was well synthesized and purified.

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