

## Article

# Response Surface Optimization of Croscarmellose Sodium Synthesis: Influence of Crosslinking Parameters on Swelling and Water Retention Properties

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## Abstract

Croscarmellose sodium (CCS) is a crosslinked cellulose-based superdisintegrant, widely utilized to enhance the disintegration and dissolution behavior of drugs from pharmaceutical solid dosage forms. In the present study, CCS was synthesized through controlled crosslinking of sodium carboxymethyl cellulose (CMC) by one-step synthesis and optimized using Response Surface Methodology (RSM) based on the Box–Behnken Design (BBD). The effects of four independent variables, namely isopropyl alcohol (IPA) concentration (70–100% *v/v*), reaction time (2–4 h), reaction temperature (50–70 °C), and concentration of crosslinking agent (CLA) (glycolic acid used as the CLA) (10–20% *w/w* of CMC weight), on swelling index (SI) and water retention capacity (WRC) of synthesized CCS were systematically evaluated. A total of 29 experimental runs, each representing a unique combination of reaction conditions generated by a three-level Box–Behnken Design (BBD) using Design-Expert<sup>®</sup> software, were conducted to synthesize CCS samples. SI and WRC of each synthesized CCS sample were subsequently measured and used to develop statistically validated predictive models and identify the optimal synthesis conditions. The successful formation of croscarmellose sodium was critically confirmed by Fourier Transform Infrared (FTIR) spectroscopy. Analysis of variance (ANOVA) demonstrated that the developed models were statistically significant, with good predictive capability for both swelling index and water retention responses. A quadratic model adequately described the swelling index ( $R^2 = 0.9041$ , adjusted  $R^2 = 0.8083$ ,  $p < 0.0001$ ), whereas a linear model was selected for WRC ( $R^2 = 0.6112$ , adjusted  $R^2 = 0.5463$ ,  $p < 0.0001$ ). Reaction time and CLA concentration exhibited substantial influence on the functional properties of the synthesized CCS compared to other factors. The optimized synthesis conditions were identified as 93.23% IPA concentration, 4 h reaction time, 70 °C reaction temperature, and 10% CLA concentration. Under these conditions, the predicted swelling index and water retention capacity were 7.529 mL/g and 443.85%, respectively. Response surface analysis further revealed significant interaction effects among the synthesis variables, particularly between IPA concentration and reaction time. The findings of this study demonstrate that



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RSM-BBD is an effective statistical approach for optimizing cellulose-based superdisintegrant synthesis and provide valuable insights into the structure–property relationships governing the hydration and swelling behavior of CCS. The optimized CCS synthesized in this research thus shows potential for application as a high-performance pharmaceutical superdisintegrant in immediate-release tablet formulations.

**Keywords:** carboxymethyl cellulose; sodium croscarmellose; crosslinking agent; water retention capacity; swelling property

## 1. Introduction

Pharmaceutical solid dosage forms, particularly tablets, are predominantly used as a drug delivery system owing to their convenience, cost-effectiveness, dose accuracy, stability and high patient adherence [1]. Despite significant advances in pharmaceutical manufacturing technologies, the production of tablet dosage forms shows numerous obstacles, mostly due to the diversity of active pharmaceutical ingredients, variability in excipient functionality, increasing complex formulation requirements and the need to ensure consistent product quality under quality-by-design (QbD) principles [2]. These challenges have become greatly important with the adoption of advanced manufacturing strategies and continuous processing technologies, emphasizing the critical role of excipient selection and process optimization to achieve robust tablet performance [3].

However, the efficiency of drug delivery largely depends on the disintegration and dissolution of the tablet in the gastrointestinal tract, which directly affects bioavailability and therapeutic efficacy [4]. Recent studies have shown that tablet disintegration depends not only on the physicochemical characteristics of the formulation ingredients but also on the tablet's microstructure [5], manufacturing process, and the functional performance of excipients [6]. Consequently, disintegrants, especially superdisintegrants, are critical excipients that ensure rapid fragmentation of the tablet matrix and prompt release of the active pharmaceutical ingredient [7]. Disintegrating agents play a vital role in the breakdown of tablet dosage forms into smaller particles by water uptake, swelling and capillary action [8]. Thus, they facilitate a faster rate of dissolution and improve the performance, making them a fundamental ingredient utilized in immediate-release tablet production [9].

Among the various superdisintegrants available, croscarmellose sodium (CCS) has attracted considerable attention due to its water insolubility, hydrophilicity, high swelling index, and extensive absorbent properties [10]. CCS is a crosslinked polymer of sodium carboxymethyl cellulose that rapidly provides exceptional swelling characteristics due to its excellent water-wicking capabilities, resulting in efficient tablet disintegration [11]. It is frequently used in tablet formulations at concentrations ranging from 0.5 to 5.0% [12], where it imparts disintegration properties, thus enhancing dissolution and bioavailability of drugs in different tablet formulations [13]. The rapid breakdown of the tablets by CCS when exposed to water is due to its high capillary and swelling effects [14]. The disintegration property of CCS is strongly dependent on its degree of substitution, crosslink density, viscosity, and swelling index, which strongly depend on synthesis parameters, including reaction temperature, crosslinking agent concentration, solvent composition and reaction time [15]. Therefore, optimizing these parameters is crucial to achieving a consistent and high-performance superdisintegrant [16]. Variations in synthesis conditions can significantly influence CCS quality, leading to inconsistent disintegration behavior in tablet formulations [17].

Several studies have investigated the synthesis and characterization of croscarmellose sodium using different cellulose sources, crosslinking agents, and reaction conditions, demonstrating that the functional properties of CCS are highly dependent on the synthesis process. Previous investigations are based on a multi-step synthesis process. Additionally, previous studies have shown that reaction temperature, crosslinking degree, reaction time, and solvent composition significantly influence the swelling behavior, water uptake, and physicochemical properties of CCS [18]. However, many of these studies primarily employed the conventional one-factor-at-a-time (OFAT) approach or evaluated individual synthesis variables independently, without systematically investigating the interactions among multiple process parameters. Consequently, the combined influence of critical synthesis variables on CCS performance remains insufficiently understood, limiting the development of robust and reproducible synthesis protocols.

Traditional optimization methods, such as the one-factor-at-a-time (OFAT) approach, are inefficient and also fail to identify interactions among factors. Instead, Response Surface Methodology (RSM) is a more efficient and systematic approach by enabling the simultaneous evaluation of multiple parameters and their interactions while minimizing the number of experimental trials required [19]. Among the various RSM designs, the Box–Behnken Design (BBD) is particularly advantageous because of fewer experimental runs, avoiding extreme factor combinations, and efficiently fitting quadratic models (second-order polynomial models) [20]. The BBD approach, which consists of a nonlinear model, has been successfully applied in optimizing numerous pharmaceutical processes, including polymer synthesis, nanoparticle formulation, and analytical method development [21]. Optimizing process parameters and their associated response variables in an output–input relationship is the main goal of this technique [22]. The primary objective of this methodology is to establish quantitative relationships between process variables and response parameters, thereby facilitating prediction and optimization of the product performance of synthesized croscarmellose sodium through a one-step synthesis process.

Therefore, the present study employed Response Surface Methodology based on a Box–Behnken design to systematically optimize the synthesis of croscarmellose sodium by evaluating the combined effects of isopropyl alcohol concentration, reaction time, reaction temperature, and crosslinking agent concentration on swelling index and water retention capacity of the synthesized croscarmellose sodium produced through a one-step synthesis process. Unlike conventional optimization approaches, this multivariate strategy enables the development of predictive mathematical models while accounting for interactions among synthesis variables. The findings of this study provide a statistically validated framework for optimizing CCS synthesis and contribute to the development of high-performance pharmaceutical superdisintegrant with improved functional properties.

## 2. Materials and Methods

### 2.1. Materials

The materials used in this research, including sodium carboxymethyl cellulose (CMC; degree of substitution 0.8) and croscarmellose sodium (standard), were obtained from Beximco Pharmaceuticals Ltd., Tongi, Gazipur, Bangladesh as gifts. The isopropyl alcohol (IPA) (HPLC Grade), sulfuric acid (98% *w/v* solution), glycolic acid 70% (*w/v*) in water solution (used as the crosslinking agent (CLA)) were procured from the local supplier of Merck KGaA, Darmstadt, Germany.

### 2.2. Experimental Design

Response Surface Methodology (RSM) based on BBD was employed to assess the effects of four independent variables on the synthesis and physiochemical and functional

properties of croscarmellose sodium (Table 1). The independent variables included isopropyl alcohol (IPA) concentration (A), reaction time (B), reaction temperature (C) and crosslinking agent (CLA) (glycolic acid as the CLA) concentration (% of CMC) (D) on the swelling index and water retention capacity of the synthesized croscarmellose sodium. The ranges of IPA concentration (70–100%, *v/v*), reaction time (2–4 h), reaction temperature (50–70 °C), and glycolic acid concentration (10–20%, *w/w* of CMC) were selected based on preliminary experimental trials. Changing the reaction time, temperature or CLA or IPA concentration beyond the set value provided lower values of the swelling index and water retention capacity of CCS. Each factor was investigated at three coded levels (−1, 0 and +1), representing low, medium and high, respectively.

**Table 1.** Variables modified during synthesis of CCS.

| Symbols | Variables                    | Units           | Range and Levels |    |     |
|---------|------------------------------|-----------------|------------------|----|-----|
|         |                              |                 | −1               | 0  | +1  |
| A       | Conc. of IPA                 | % <i>v/v</i>    | 70               | 85 | 100 |
| B       | Reaction time                | hr              | 2                | 3  | 4   |
| C       | Temperature                  | °C              | 50               | 60 | 70  |
| D       | Conc. of CLA (glycolic acid) | % of CMC weight | 10               | 15 | 20  |

Using Design-Expert® software (Version 13, Stat-Ease Inc., Minneapolis, MN, USA), 29 experimental runs were generated. All experiments were performed in triplicate to ensure reproducibility and reliability of the results. The mean swelling index and water retention capacity were taken into consideration. The effects of the independent variables on two response parameters, namely swelling index and water retention capacity, were evaluated. The experimental data were fitted to first-order (linear) and second-order (quadratic) polynomial models to identify the effects of the independent variables on response.

The response surface analysis was based on a generalized first-order polynomial model, expressed as Equation (1), and a generalized second-order polynomial model, expressed as Equation (2):

$$Y = \beta_0 + \sum_{i=1}^n \beta_i X_i \quad (1)$$

$$Y = \beta_0 + \sum_{i=1}^n \beta_i X_i + \sum_{i=1}^n \beta_{ii} X_i^2 + \sum_{i < j}^n \beta_{ij} X_i X_j \quad (2)$$

where Y indicates the response variables (swelling index or water retention capacity);  $\beta_0$  denotes the intercept;  $\beta_i X_i$ ,  $\beta_{ii}$  and  $\beta_{ij}$  indicate the linear, quadratic and interaction coefficients, respectively;  $X_i$  and  $X_j$  refer to the independent variables [23,24].

The experimental data were analyzed by Design-Expert software (Version 13, Stat-Ease Inc., USA) using the BBD approach, and regression models were developed for swelling index (SI) and water retention capacity (WRC). Model adequacy and statistical significance were evaluated using the ANOVA, based on the F-values, *p*-values and the coefficient of determination ( $R^2$ , adjusted  $R^2$ , and predicted  $R^2$ ). The suitability of the models was further confirmed by lack-of-fit tests, coefficient of variation (CV%), and adequate precision values. Finally, three-dimensional response surface plots were used to assess the interaction effects of the factors on dependent variables, and numerical optimization within the software was used to identify the operating parameters that enhance efficiency [25]. Based on the results, a second-order polynomial equation was generated to determine the optimum point. Design-Expert software was used for model fitting, statistical analysis, and evaluation of the effects of different factors.

### 2.3. Synthesis of Croscarmellose Sodium

For the synthesis of croscarmellose sodium, 60 mL media containing different concentrations of IPA (% *v/v*) was taken. For example, in the case of 85% IPA-containing media, 51 mL of HPLC-grade IPA was mixed with 9 mL of distilled water. Then, a few drops (2–3 drops) of 1N H<sub>2</sub>SO<sub>4</sub> solution was used to adjust the pH of the media to 1.5–2.0. After that, 6 g of CMC was added to the media at different concentrations (% *v/v*) of IPA (HPLC-grade) in distilled water. The media was stirred at room temperature for 30 min at 250 rpm in a hotplate magnetic stirrer (Model no. MS7-H550-Pro, ONiLAB LLC, Calabasas, CA, USA). Then, the temperature of the mixture was raised to the targeted reaction temperature, and a specified volume of glycolic acid as the crosslinking agent (CLA) was added to the mixture. This was stirred at 500 rpm for 2 to 4 h, and then cooled to room temperature (Table 2). The volume of glycolic acid solution required in the reaction was calculated according to the target glycolic acid concentration relative to the weight of sodium carboxymethyl cellulose (CMC). Initially, the amount of pure glycolic acid needed was determined as a percentage of the CMC weight. Since glycolic acid was available as a 70% (*w/v*) solution (equivalent to 70 g of glycolic acid per 100 mL of solution), the calculated mass of glycolic acid was converted into the corresponding solution volume required for the reaction. After cooling, the mixture was filtered, washed with 100 mL IPA thrice, and dried at 60 °C in an oven dryer (JS Research Inc., Gongju-city, Republic of Korea) until constant weight of the croscarmellose sodium in powder form was obtained.

**Table 2.** Box–Behnken design matrix showing experimental conditions for croscarmellose sodium (CCS) synthesis.

| Experiment No. | Conc. of IPA (% <i>v/v</i> ) | Reaction Time (h) | Temperature (°C) | Conc. of CLA (% of CMC Weight) |
|----------------|------------------------------|-------------------|------------------|--------------------------------|
| 1              | 85                           | 3                 | 50               | 10                             |
| 2              | 100                          | 3                 | 70               | 15                             |
| 3              | 85                           | 2                 | 60               | 10                             |
| 4              | 70                           | 3                 | 50               | 15                             |
| 5              | 85                           | 3                 | 70               | 10                             |
| 6              | 85                           | 2                 | 70               | 15                             |
| 7              | 85                           | 2                 | 50               | 15                             |
| 8              | 85                           | 3                 | 60               | 15                             |
| 9              | 85                           | 3                 | 60               | 15                             |
| 10             | 85                           | 3                 | 60               | 15                             |
| 11             | 85                           | 4                 | 70               | 15                             |
| 12             | 85                           | 4                 | 60               | 20                             |
| 13             | 70                           | 4                 | 60               | 15                             |
| 14             | 70                           | 2                 | 60               | 15                             |
| 15             | 85                           | 4                 | 50               | 15                             |
| 16             | 85                           | 3                 | 50               | 20                             |
| 17             | 85                           | 2                 | 60               | 20                             |
| 18             | 85                           | 3                 | 60               | 15                             |
| 19             | 85                           | 3                 | 70               | 20                             |
| 20             | 85                           | 3                 | 60               | 15                             |

Table 2. Cont.

| Experiment No. | Conc. of IPA (% v/v) | Reaction Time (h) | Temperature (°C) | Conc. of CLA (% of CMC Weight) |
|----------------|----------------------|-------------------|------------------|--------------------------------|
| 21             | 70                   | 3                 | 60               | 20                             |
| 22             | 100                  | 3                 | 60               | 10                             |
| 23             | 100                  | 3                 | 60               | 20                             |
| 24             | 70                   | 3                 | 70               | 15                             |
| 25             | 70                   | 3                 | 60               | 10                             |
| 26             | 85                   | 4                 | 60               | 10                             |
| 27             | 100                  | 3                 | 50               | 15                             |
| 28             | 100                  | 4                 | 60               | 15                             |
| 29             | 100                  | 2                 | 60               | 15                             |

#### 2.4. FTIR Analysis

The synthesized croscarmellose sodium was dried properly and subjected to FTIR analysis for spectra using an IRSpirit spectrophotometer (Shimadzu Corporation, Koyto, Japan). Spectra were recorded in transmission mode with 20 scans. The scans were taken within the frequency range of 4000–650 cm<sup>−1</sup> [17].

#### 2.5. Measurement of Swelling Index

To measure the swelling index of synthesized CCS, 9 mL of 0.1N HCl (mimicking the stomach pH) was taken in a 10 mL measuring cylinder (in every case) and 0.5 g of dried croscarmellose sodium was added to the cylinder slowly from the top. It was then kept standing for 5 min. The volume taken by swelled croscarmellose sodium in the measuring cylinder was checked and recorded after 5 min. [26]. The SI was express as mL/g.

$$\text{Swelling index} = \frac{\text{Volume of CCS after 5 min (mL)}}{\text{weight of the dry CSS taken (g)}} \quad (3)$$

#### 2.6. Determination of Water Retention Capacity (WRC)

A clean and dry blank centrifuge tube was first weighed ( $w_1$ ). Subsequently, 0.1 g of CCS was added to the tube, and the weight of the tube containing dry CCS was measured ( $w_2$ ). Thereafter, 800 µL of 0.1N HCl was added to the tube, and the mixture was vortexed thoroughly to ensure complete wetting of the sample. The tube was then centrifuged at 5000 rpm for 5 min. After centrifugation, the supernatant was carefully removed completely, and the weight of the tube containing wet CCS was measured ( $w_3$ ).

Calculation of the WRC was carried out using Equation (4).

$$\text{Water Retention Capacity} = \frac{w_3 - w_2}{w_2 - w_1} 100\% \quad (4)$$

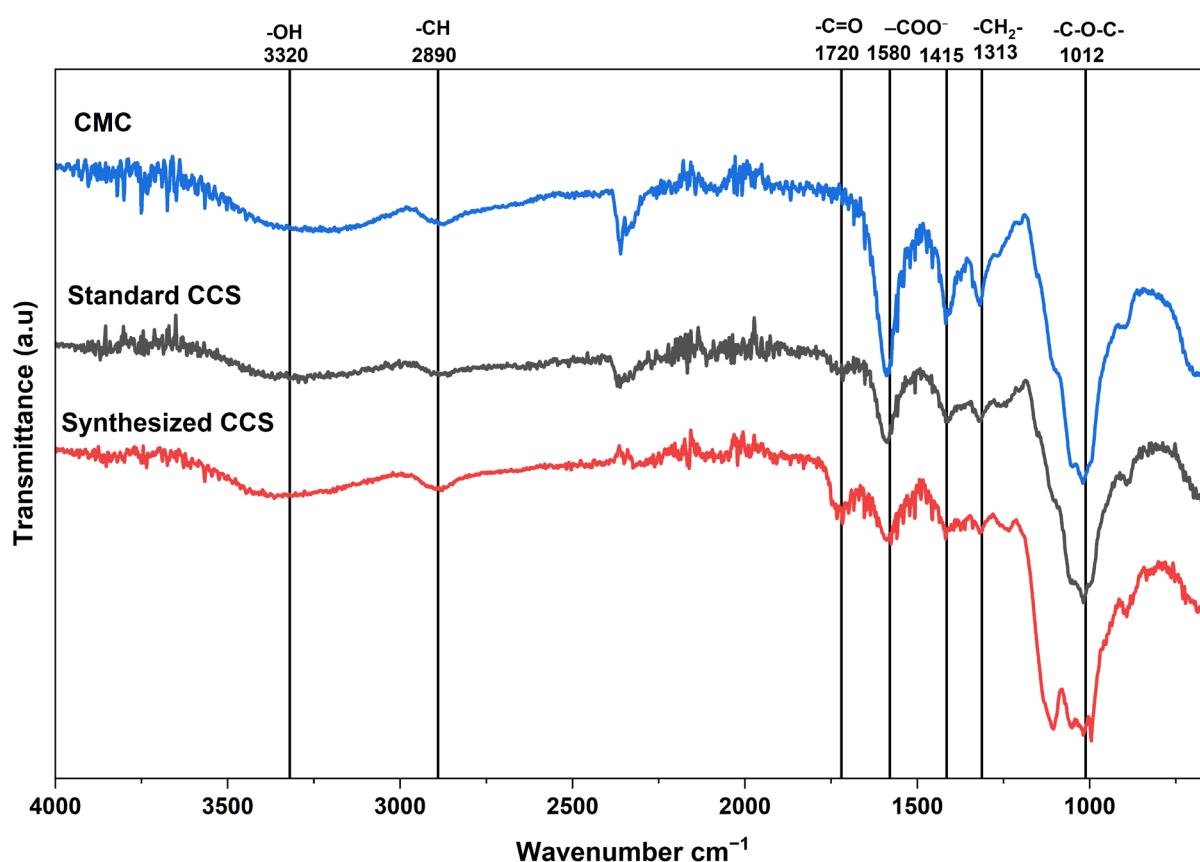
where  $w_1$  is the weight of the empty centrifuge tube (g),  $w_2$  is the weight of the centrifuge tube containing the dry CCS sample (g), and  $w_3$  is the weight of the centrifuge tube containing the wet CCS after removal of the supernatant (g). The WRC is expressed as a percentage (%) [27].

### 3. Results and Discussion

The synthesized product was preliminarily characterized by its organoleptic properties and solubility in water. Compared with the starting sodium carboxymethyl cellulose (CMC), which readily dissolved in water to form a viscous solution, the synthesized product appeared as a white to off-white, odorless, fibrous powder that was insoluble in water but readily swelled to form a uniform dispersion. This change in water behavior is consistent with the formation of crosslinked croscarmellose sodium (CCS). The successful conversion of CMC to CCS was subsequently confirmed by FTIR analysis.

#### 3.1. Identification by FT-IR

The FT-IR spectra of CMC, standard CCS and synthesized CCS were recorded within the 4000 to 650  $\text{cm}^{-1}$  frequency range in transmission mode and are presented in Figure 1. The synthesized product exhibited the characteristic absorption bands of cellulose derivatives and showed a spectral profile closely comparable to that of the standard CCS.



**Figure 1.** FT-IR spectra of carboxymethyl cellulose (CMC), standard CCS, and synthesized CCS.

The broad absorption band observed within 3200–3600  $\text{cm}^{-1}$  was observed for all samples and is attributed to the stretching vibration of hydroxyl ( $-\text{OH}$ ) groups, which is associated with the cellulose structure and due to intermolecular hydrogen bonding [28]. The absorption band at 2850–2950  $\text{cm}^{-1}$  corresponds to the stretching vibration of aliphatic C–H bonds, whereas the band in the 1300–1450  $\text{cm}^{-1}$  region is assigned to the bending vibration of methylene ( $-\text{CH}_2-$ ) groups, both of which are characteristic of cellulose derivatives [29]. The characteristic asymmetric and symmetric stretching vibrations of the carboxylate ( $-\text{COO}^-$ ) groups were observed at approximately 1560–1610  $\text{cm}^{-1}$  and 1410–1450  $\text{cm}^{-1}$ , respectively, confirming the presence of sodium carboxymethyl substituents in both the standard and synthesized CCS [30]. Furthermore, the intense ab-

sorption band in the 1000–1150  $\text{cm}^{-1}$  region corresponds to the C–O–C stretching vibration of the  $\beta$ -(1→4)-glycosidic ether linkage, demonstrating that the cellulose framework was retained throughout the synthesis.

A distinct absorption band was seen in the 1700–1750  $\text{cm}^{-1}$  region in the synthesized CCS. In contrast, a weak band was found in the case of the standard CCS in this region. There is no peak for CMC within this region. This peak is attributed to the stretching vibration of ester carbonyl (C = O) groups formed through the reaction between the hydroxyl group of CMC and the carboxyl groups of glycolic acid [31]. The weak absorption peak within 2200–2400  $\text{cm}^{-1}$  in all spectra is attributed to atmospheric carbon dioxide during FT-IR measurement and is not associated with the chemical structure of CCS [32]. The close similarity between the FT-IR spectra of the synthesized sample and the standard CCS, together with the appearance of ester carbonyl absorption in the synthesized product, indicates that the sample produced using this method is glycolic acid-crosslinked croscarmellose sodium while preserving the characteristic structural features of cellulose and sodium carboxymethyl cellulose.

### 3.2. Experimental Responses of Swelling Index and Water Retention Capacity

The experimental responses for the swelling index (SI) and water retention capacity (WRC) of the synthesized croscarmellose sodium (CCS), expressed as mean  $\pm$  standard deviation (SD) from triplicate experiments, are presented in Table 3.

**Table 3.** Experimental responses of the synthesized croscarmellose sodium (CCS): swelling index (SI) and water retention capacity (WRC) obtained from the Box–Behnken design experiments.

| Experiment No. | Swelling Index (Mean $\pm$ SD)<br>mL/g | Water Retention Capacity<br>(Mean $\pm$ SD)<br>(%) |
|----------------|----------------------------------------|----------------------------------------------------|
| 1              | 6.5 $\pm$ 0.08                         | 305.662 $\pm$ 8.825                                |
| 2              | 6.2 $\pm$ 0.07                         | 336.475 $\pm$ 9.965                                |
| 3              | 6.2 $\pm$ 0.09                         | 279.617 $\pm$ 10.781                               |
| 4              | 5.6 $\pm$ 0.13                         | 289.007 $\pm$ 8.235                                |
| 5              | 7.4 $\pm$ 0.12                         | 443.853 $\pm$ 9.358                                |
| 6              | 6.2 $\pm$ 0.12                         | 294.763 $\pm$ 7.151                                |
| 7              | 5.4 $\pm$ 0.11                         | 275.291 $\pm$ 11.616                               |
| 8              | 6.8 $\pm$ 0.09                         | 341.845 $\pm$ 8.182                                |
| 9              | 6.6 $\pm$ 0.11                         | 325.284 $\pm$ 4.964                                |
| 10             | 7.2 $\pm$ 0.10                         | 367.448 $\pm$ 6.425                                |
| 11             | 7.0 $\pm$ 0.14                         | 438.155 $\pm$ 11.821                               |
| 12             | 6.8 $\pm$ 0.08                         | 359.770 $\pm$ 9.714                                |
| 13             | 5.7 $\pm$ 0.13                         | 291.754 $\pm$ 8.367                                |
| 14             | 5.4 $\pm$ 0.12                         | 274.808 $\pm$ 4.846                                |
| 15             | 7.0 $\pm$ 0.11                         | 389.850 $\pm$ 6.942                                |
| 16             | 6.0 $\pm$ 0.12                         | 312.488 $\pm$ 3.952                                |
| 17             | 5.4 $\pm$ 0.09                         | 255.043 $\pm$ 9.467                                |
| 18             | 6.4 $\pm$ 0.11                         | 303.324 $\pm$ 8.583                                |
| 19             | 6.4 $\pm$ 0.08                         | 307.625 $\pm$ 10.642                               |
| 20             | 7.3 $\pm$ 0.09                         | 399.425 $\pm$ 9.213                                |

Table 3. *Cont.*

| Experiment No. | Swelling Index (Mean $\pm$ SD)<br>mL/g | Water Retention Capacity<br>(Mean $\pm$ SD)<br>(%) |
|----------------|----------------------------------------|----------------------------------------------------|
| 21             | 5.2 $\pm$ 0.09                         | 221.006 $\pm$ 9.055                                |
| 22             | 7.2 $\pm$ 0.11                         | 374.474 $\pm$ 8.124                                |
| 23             | 5.6 $\pm$ 0.08                         | 292.079 $\pm$ 6.913                                |
| 24             | 6.4 $\pm$ 0.11                         | 361.612 $\pm$ 10.826                               |
| 25             | 5.6 $\pm$ 0.08                         | 293.404 $\pm$ 8.212                                |
| 26             | 7.6 $\pm$ 0.07                         | 429.228 $\pm$ 8.145                                |
| 27             | 6.6 $\pm$ 0.11                         | 322.459 $\pm$ 4.758                                |
| 28             | 6.8 $\pm$ 0.10                         | 350.541 $\pm$ 7.522                                |
| 29             | 5.6 $\pm$ 0.10                         | 288.815 $\pm$ 4.036                                |

The SI values ranged from 5.2  $\pm$  0.3 to 7.6  $\pm$  0.2 mL/g, whereas the WRC values ranged from 221.006  $\pm$  9.057% to 443.853  $\pm$  13.351%, demonstrating that the synthesis conditions markedly influenced the hydration and water retention characteristics of the synthesized CCS. The highest SI (7.6  $\pm$  0.2 mL/g) was obtained in Experiment 26, which was synthesized using 85% isopropyl alcohol (IPA), 4 h reaction time, 60 °C, and 10% glycolic acid (CLA, based on CMC weight). The highest WRC (443.853  $\pm$  13.351%) was observed in Experiment 5, prepared under 85% IPA, 3 h reaction time, 70 °C, and 10% CLA. Conversely, the lowest SI (5.2  $\pm$  0.3 mL/g) and the lowest WRC (221.006  $\pm$  9.057%) were both recorded in Experiment 21, synthesized using 70% IPA, 3 h reaction time, 60 °C, and 20% CLA.

Overall, these results demonstrate that the selected synthesis parameters exerted a substantial influence on the swelling and water-retention behavior of CCS. The broad variation in SI and WRC values obtained from the Box–Behnken experimental design provided a robust dataset for Response Surface Methodology (RSM), facilitating the development of predictive models and the determination of the optimum synthesis conditions [33].

### 3.3. Design of Box–Behnken Model on Swelling Index

The conditions of Box–Behnken experimental design and results from the experiments are shown in Tables 2 and 3. There were noticeable differences in the swelling index of CCS samples with different experimental conditions.

Based on the experimental results, regression analysis was done and a second-order polynomial equation was generated, which describes the relationship between the independent variables and the swelling index of CCS, as shown in Equation (5).

$$\begin{aligned} \text{Swelling Index} = & 6.86 + 0.34A + 0.56B + 0.21C - 0.43D + 0.23AB - 0.3AC \\ & - 0.3AD - 0.2BC - 0.13CD - 0.68A^2 - 0.28B^2 - 0.08C^2 - 0.18D^2 \end{aligned} \quad (5)$$

where A, B, C and D denote the coded levels of independent variables: conc. of IPA ( $v/v$ ), reaction time, temperature and conc. of CLA (glycolic acid ( $w/w$  of CMC)), respectively.

The suitability of different regression models for predicting the swelling index was assessed using sequential model fitting and is presented in Table 4.

**Table 4.** Sequential model fitting for swelling index.

| Source                             | Sum of Squares | DF             | Mean Square             | F-Value                  | p-Value  |           |
|------------------------------------|----------------|----------------|-------------------------|--------------------------|----------|-----------|
| Sequential sum of squares          |                |                |                         |                          |          |           |
| Mean                               | 1168.72        | 1              | 1168.72                 |                          |          |           |
| Linear                             | 7.83           | 4              | 1.96                    | 8.27                     | 0.0002 * |           |
| 2FI                                | 1.15           | 6              | 0.1908                  | 0.7570                   | 0.6124   |           |
| Quadratic                          | 3.24           | 4              | 0.8105                  | 8.76                     | 0.0009 * | Suggested |
| Cubic                              | 0.5400         | 8              | 0.0675                  | 0.5362                   | 0.7967   | Aliased   |
| Residual                           | 0.7553         | 6              | 0.1259                  |                          |          |           |
| Total                              | 1182.23        | 29             | 40.77                   |                          |          |           |
| Lack-of-fit tests                  |                |                |                         |                          |          |           |
| Linear                             | 5.09           | 20             | 0.2545                  | 1.72                     | 0.3205   |           |
| 2FI                                | 3.95           | 14             | 0.2818                  | 1.90                     | 0.2809   |           |
| Quadratic                          | 0.7033         | 10             | 0.0703                  | 0.4752                   | 0.8450   | Suggested |
| Cubic                              | 0.1633         | 2              | 0.0817                  | 0.5518                   | 0.6143   | Aliased   |
| Pure Error                         | 0.5920         | 4              | 0.1480                  |                          |          |           |
| Model summary statistics           |                |                |                         |                          |          |           |
|                                    | Std. Dev.      | R <sup>2</sup> | Adjusted R <sup>2</sup> | Predicted R <sup>2</sup> | PRESS    |           |
| Linear                             | 0.4866         | 0.5795         | 0.5094                  | 0.4106                   | 7.96     |           |
| 2FI                                | 0.5021         | 0.6642         | 0.4777                  | 0.2014                   | 10.79    |           |
| Quadratic                          | 0.3042         | 0.9041         | 0.8083                  | 0.6317                   | 4.98     | Suggested |
| Cubic                              | 0.3548         | 0.9441         | 0.7391                  | −0.8091                  | 24.44    | Aliased   |
| Fit statistics for quadratic model |                |                |                         |                          |          |           |
| C.V. %                             |                |                |                         |                          | 4.79     |           |
| Adeq Precision                     |                |                |                         |                          | 9.8661   |           |

\* Statistically significant:  $p < 0.05$ .

Sequential model fitting analysis for swelling index indicated that the quadratic model was the most appropriate model, with a statistically significant  $p$  value of 0.0009 and  $F$  value of 8.76. The lack-of-fit test results for the quadratic model are not significant ( $p$  value = 0.6124), confirming that the quadratic model is adequately fit for the experiment.

The adequacy and validity of the models were evaluated by performing analysis of variance (ANOVA), as shown in Table 5.

According to the statistical results, the proposed model has a high degree of fit for the swelling index. The model  $F$ -value (9.43) and the associated  $p$ -value ( $p < 0.0001$ ) indicate that the regression model was significant. There is only a 0.01% chance that an  $F$ -value this large could occur due to noise [34].  $p$ -values less than 0.05 indicate model terms are significant. In this case, linear term A (IPA concentration), B (reaction time), C (temperature), D (CLA (glycolic acid) concentration) and the quadratic terms  $A^2$  and  $B^2$  are significant model terms. The lack of fit is not significant ( $p$  value = 0.8450), with an  $F$ -value of 0.48, which suggests that the model adequately represents the experimental data [35]. A non-significant lack of fit is desirable because it suggests that the residual variation is primarily due to random experimental error rather than model inadequacy [36].

**Table 5.** ANOVA for swelling index.

| Source         | Sum of Squares | Degree of Freedom | Mean Square | F-Value | p-Value   |                 |
|----------------|----------------|-------------------|-------------|---------|-----------|-----------------|
| Model          | 12.22          | 14                | 0.8726      | 9.43    | <0.0001 * | Significant     |
| A              | 1.40           | 1                 | 1.40        | 15.14   | 0.0016 *  |                 |
| B              | 3.74           | 1                 | 3.74        | 40.43   | <0.0001 * |                 |
| C              | 0.5208         | 1                 | 0.5208      | 5.63    | 0.0325 *  |                 |
| D              | 2.17           | 1                 | 2.17        | 23.43   | 0.0003 *  |                 |
| AB             | 0.2025         | 1                 | 0.2025      | 2.19    | 0.1612    |                 |
| AC             | 0.3600         | 1                 | 0.3600      | 3.89    | 0.0686    |                 |
| AD             | 0.3600         | 1                 | 0.3600      | 3.89    | 0.0686    |                 |
| BC             | 0.1600         | 1                 | 0.1600      | 1.73    | 0.2096    |                 |
| BD             | 0.0000         | 1                 | 0.0000      | 0.0000  | 1.0000    |                 |
| CD             | 0.0625         | 1                 | 0.0625      | 0.6755  | 0.4249    |                 |
| A <sup>2</sup> | 3.04           | 1                 | 3.04        | 32.82   | <0.0001 * |                 |
| B <sup>2</sup> | 0.5238         | 1                 | 0.5238      | 5.66    | 0.0321 *  |                 |
| C <sup>2</sup> | 0.0460         | 1                 | 0.0460      | 0.4966  | 0.4925    |                 |
| D <sup>2</sup> | 0.2200         | 1                 | 0.2200      | 2.38    | 0.1454    |                 |
| Residual       | 1.30           | 14                | 0.0925      |         |           |                 |
| Lack of Fit    | 0.7033         | 10                | 0.0703      | 0.4752  | 0.8450    | Not significant |
| Pure Error     | 0.5920         | 4                 | 0.1480      |         |           |                 |
| Cor Total      | 13.51          | 28                |             |         |           |                 |

\* Statistically significant:  $p < 0.05$ .

The model exhibited a high coefficient of determination ( $R^2 = 0.9041$ ), indicating strong agreement between the predicted and experimental responses. Furthermore, the adjusted  $R^2$  value of 0.8083 reveals that approximately 81% of the variability in the swelling index was explained by the model, demonstrating a good level of predictive accuracy for optimization studies. The difference between the adjusted  $R^2$  and predicted  $R^2$  values was less than 0.20, indicating satisfactory agreement and a reliable relationship between the response and the independent variables [37].

In addition, the low coefficient of variation (CV) value of 4.79% reflects the high precision and reproducibility of the experimental results [38]. The adequate precision value of 9.866, which is well above the minimum desirable value of 4, indicates an adequate signal-to-noise ratio and confirms the suitability of the model for navigating the design space and predicting process performance during optimization [39].

### 3.4. Design of Box–Behnken Model on Water Retention Capacity

Based on the experimental results, regression analysis was performed to establish the relationship between the independent variables and water retention capacity of CCS.

The relationship is expressed by the following first-order polynomial equation (linear model) (Equation (6)):

$$\text{WRC} = 328.45 + 19.44A + 49.25B + 23.98C - 31.52D \quad (6)$$

where A, B, C, and D denote the coded levels of isopropyl alcohol (IPA) concentration ( $v/v$ ), reaction time, temperature, and glycolic acid (CLA) concentration ( $w/w$  of CMC), respectively.

The suitability of different regression models for water retention capacity was evaluated and is presented in Table 6.

**Table 6.** Sequential model fitting for water retention capacity.

| Source                          | Sum of Squares      | DF             | Mean Square             | F-Value                  | <i>p</i> -Value |           |
|---------------------------------|---------------------|----------------|-------------------------|--------------------------|-----------------|-----------|
| Sequential sum of squares       |                     |                |                         |                          |                 |           |
| Mean                            | $3.129 \times 10^6$ | 1              | $3.129 \times 10^6$     |                          |                 |           |
| Linear                          | 52,456.94           | 4              | 13,114.24               | 9.43                     | <0.0001 *       | Suggested |
| 2FI                             | 7212.06             | 6              | 1202.01                 | 0.8269                   | 0.5641          |           |
| Quadratic                       | 11,450.42           | 4              | 2862.61                 | 2.72                     | 0.0723          |           |
| Cubic                           | 8881.17             | 8              | 1110.15                 | 1.14                     | 0.4482          | Aliased   |
| Residual                        | 5832.58             | 6              | 972.10                  |                          |                 |           |
| Total                           | $3.214 \times 10^6$ | 29             | $1.108 \times 10^5$     |                          |                 |           |
| Lack-of-fit tests               |                     |                |                         |                          |                 |           |
| Linear                          | 27,805.06           | 20             | 1390.25                 | 0.9982                   | 0.5702          | Suggested |
| 2FI                             | 20,593.00           | 14             | 1470.93                 | 1.06                     | 0.5340          |           |
| Quadratic                       | 9142.58             | 10             | 914.26                  | 0.6564                   | 0.7320          |           |
| Cubic                           | 261.41              | 2              | 130.70                  | 0.0938                   | 0.9124          | Aliased   |
| Pure Error                      | 5571.17             | 4              | 1392.79                 |                          |                 |           |
| Model summary statistics        |                     |                |                         |                          |                 |           |
|                                 | Std. Dev.           | R <sup>2</sup> | Adjusted R <sup>2</sup> | Predicted R <sup>2</sup> | PRESS           |           |
| Linear                          | 37.29               | 0.6112         | 0.5463                  | 0.4332                   | 48,653.28       | Suggested |
| 2FI                             | 38.13               | 0.6952         | 0.5258                  | 0.1812                   | 70,276.28       |           |
| Quadratic                       | 32.42               | 0.8286         | 0.6572                  | 0.2851                   | 61,366.22       |           |
| Cubic                           | 31.18               | 0.9320         | 0.6829                  | 0.4600                   | 46,347.65       | Aliased   |
| Fit statistics for linear model |                     |                |                         |                          |                 |           |
| C.V. %                          |                     |                |                         |                          | 11.35           |           |
| Adeq Precision                  |                     |                |                         |                          | 10.4318         |           |

\* Statistically significant:  $p < 0.05$ .

Sequential model fitting for water retention capacity indicated that the linear model was the most suitable for the response. The linear model was statistically significant, with an F value of 9.43 and a  $p$  value of <0.0001. The linear model also showed non-significant lack of fit ( $p$  value = 0.5702). Therefore, the linear model was considered appropriate for optimizing the water retention capacity of croscarmellose sodium.

Analysis of variance (ANOVA) was used to evaluate the adequacy and predictive performance of the water retention capacity model, and the results are presented in Table 7.

**Table 7.** ANOVA for water retention capacity.

| Source          | Sum of Squares | Degree of Freedom | Mean Square | F-Value | p-Value   |                 |
|-----------------|----------------|-------------------|-------------|---------|-----------|-----------------|
| Model           | 52,456.94      | 4                 | 13,114.24   | 9.43    | <0.0001 * | Significant     |
| A—Conc. of IPA  | 4533.87        | 1                 | 4533.87     | 3.26    | 0.0835    |                 |
| B—Reaction time | 29,102.91      | 1                 | 29,102.91   | 20.93   | 0.0001 *  |                 |
| C—Temperature   | 6898.85        | 1                 | 6898.85     | 4.96    | 0.0356 *  |                 |
| D—Conc. of CLA  | 11,921.31      | 1                 | 11,921.31   | 8.57    | 0.0074 *  |                 |
| Residual        | 33,376.23      | 24                | 1390.68     |         |           |                 |
| Lack of Fit     | 27,805.06      | 20                | 1390.25     | 0.9982  | 0.5702    | Not significant |
| Pure Error      | 5571.17        | 4                 | 1392.79     |         |           |                 |
| Cor Total       | 85,833.17      | 28                |             |         |           |                 |

\* Statistically significant:  $p < 0.05$ .

The model was found to be statistically significant, as evidenced by a model F-value of 9.43 and an associated  $p$ -value of <0.0001. This indicates that the probability of obtaining a large F-value due to random experimental noise was only 0.01%. Model terms with  $p$ -values less than 0.05 were considered statistically significant contributors to water retention capacity property of CCS. Furthermore, the non-significant lack-of-fit F-value of 0.9982 demonstrated that the model adequately described the experimental data within the investigated design space and that the residual variation was primarily attributed to random error. The adjusted coefficient of determination (adjusted  $R^2 = 0.5463$ ) indicated a moderate level of model fit, suggesting that approximately 55% of the variability in water retention capacity could be explained by the selected process variables. In addition, the difference between the adjusted  $R^2$  and predicted  $R^2$  values was less than 0.20, indicating good agreement between the experimental and predicted responses and confirming the acceptable predictive performance of the model [30].

The coefficient of variation (CV) was 11.35%, indicating satisfactory experimental precision and reproducibility. Model adequacy was further supported by the adequate precision value of 10.4318, which exceeded the minimum desirable threshold of 4.0, reflecting an excellent signal-to-noise ratio. Collectively, these statistical parameters indicate that the developed model possessed adequate robustness and reliability for describing the influence of process variables on water retention capacity and can be effectively utilized for process optimization and prediction within the studied experimental domain.

### 3.5. Evaluation of Effects of Individual Factors on Swelling Index and Water Retention Capacity

The individual effects of IPA concentration, reaction time, temperature, and CLA (glycolic acid) concentration on the swelling index and water retention capacity of the synthesized croscarmellose sodium are presented in Figure 2a–h, respectively.

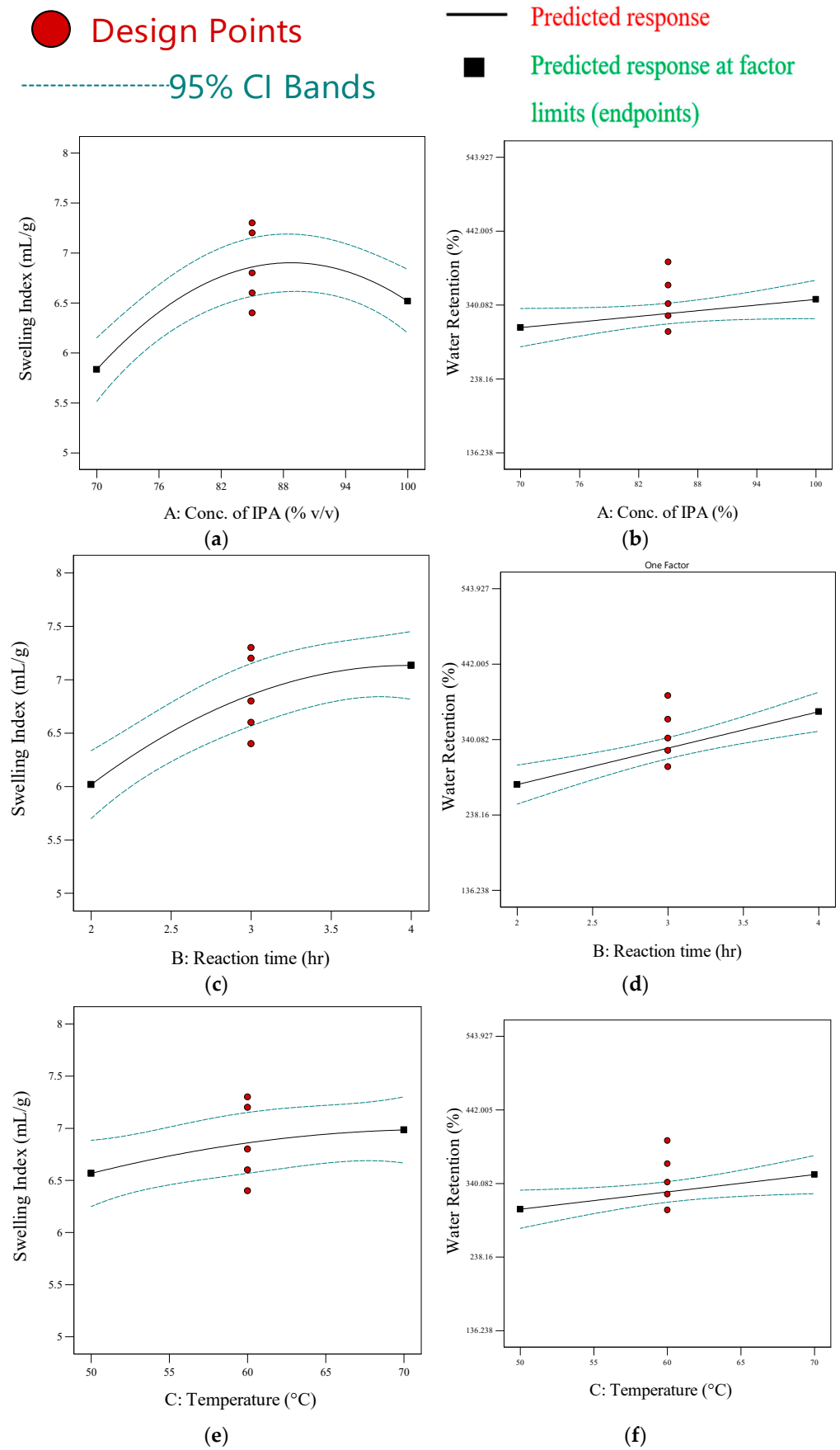
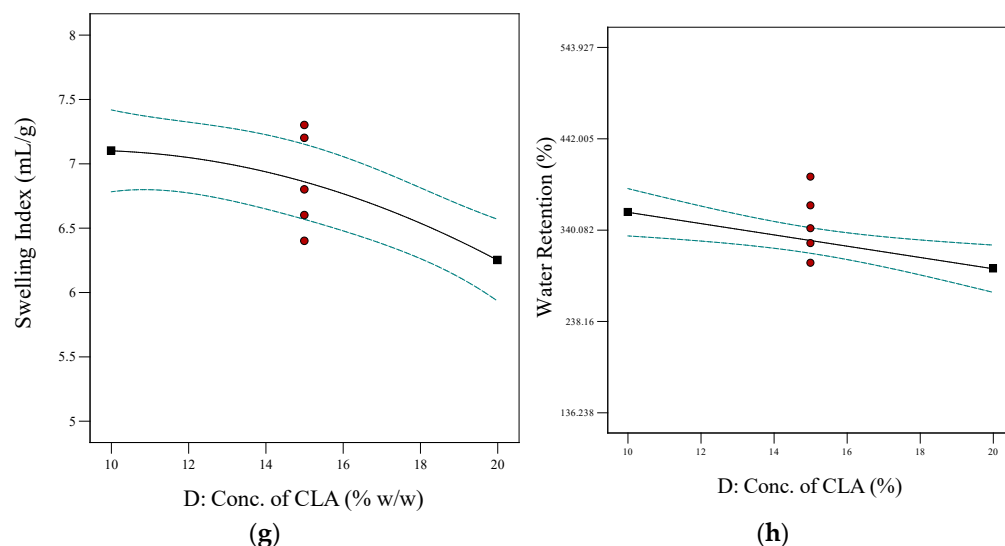


Figure 2. Cont.



**Figure 2.** One-factor response plots generated by Design-Expert® showing the effects of (a,b) IPA concentration, (c,d) reaction time, (e,f) reaction temperature, and (g,h) crosslinking agent concentration (glycolic acid) on the swelling index and water retention of the synthesized croscarmellose sodium.

### 3.5.1. Effects of IPA Concentration on Swelling Index and Water Retention Capacity

To evaluate the effects of IPA concentration, we varied the IPA concentration ( $v/v$ ) from 70% to 100% of total solvent while the reaction time (3 h), temperature (60 °C) and concentration of CLA (15%) was kept constant. As shown in Figure 2a, the response curve of the swelling index exhibits a quadratic trend, where the response initially increased with an increase in the IPA concentration, reached a maximum value and then decreased at higher concentrations. This suggests the existence of an optimum solvent polarity that promotes effective polymer network expansion. In contrast, the water retention capacity (Figure 2b) showed a positive linear trend, where it increased with the increase in IPA concentration, likely due to enhanced accessibility of hydrophilic sites.

### 3.5.2. Effects of Reaction Time on Swelling Index and Water Retention Capacity

To study the effects of reaction time on the swelling index and water retention capacity, the reaction time varied from 2 to 4 h, keeping the other parameters (IPA concentration (85%), temperature (65 °C) and CLA concentration (15%)) constant. As shown in Figure 2c, the response curve for the swelling index gradually increases, with a slight curvature at higher reaction times, suggesting continued development of the polymer network. Meanwhile, the reaction time has a linear increasing trend in relation to the water retention capacity, as shown in Figure 2d. This indicates that prolonged reaction time facilitates more effective structural rearrangement, thereby improving the hydrophilicity of CCS.

### 3.5.3. Effects of Temperature on Swelling Index and Water Retention Capacity

A range of temperatures from 50 °C to 70 °C was investigated in this study, keeping the IPA concentration (85%), reaction time (3 h) and CLA concentration (15%) fixed. The response curve of the swelling index shows a moderate positive trend (Figure 2e) with a slight curvature. There was a positive linear increasing trend, where increased water retention capacity with an increasing temperature was evident (Figure 2f).

### 3.5.4. Effects of CLA (Glycolic Acid) Concentration on Swelling Index and Water Retention Capacity

To study the effects of the CLA, the concentration was varied from 10%, 15% and 20% keeping the others factors constant. The effects of the CLA showed a negative non-

linear trend in the specified range for both the swelling index and water retention capacity (Figure 2g,h). This inverse relationship is attributed to increased crosslink density, which restricts polymer chain flexibility and reduces available free volume for water absorption, thereby limiting the swelling capacity of CCS.

### 3.6. Evaluation of Effects of Multiple Factors on Swelling Index and Water Retention Capacity

In this study, three-dimensional response surface and contour plots were used to identify the interaction effects and to determine the area of optimal reaction conditions. In this case, both linear and quadratic regression models were used to create the figures. These plots made it possible to analyze the relation between two variables and their combined impact on the swelling index and water retention capacity both visually and quantitatively while keeping the other variables constant at their central levels.

#### 3.6.1. Evaluation of Effects of Multiple Factors on Swelling Index by 3D Surface and Contour Plots for Swelling Index

##### Effects of IPA Concentration and Reaction Time on Swelling Index

As illustrated in Figure 3a, the 3D surface plot revealed a strong quadratic and interaction effect between IPA concentration and reaction time on the swelling index. Maximum swelling was observed at intermediate IPA levels combined with extended reaction time, as confirmed by elliptical contour lines (Figure 3b). At higher IPA concentrations, the swelling index decreased, likely due to reduced polymer hydration efficiency and restricted water diffusion into the polymer matrix.

#### Design Points:

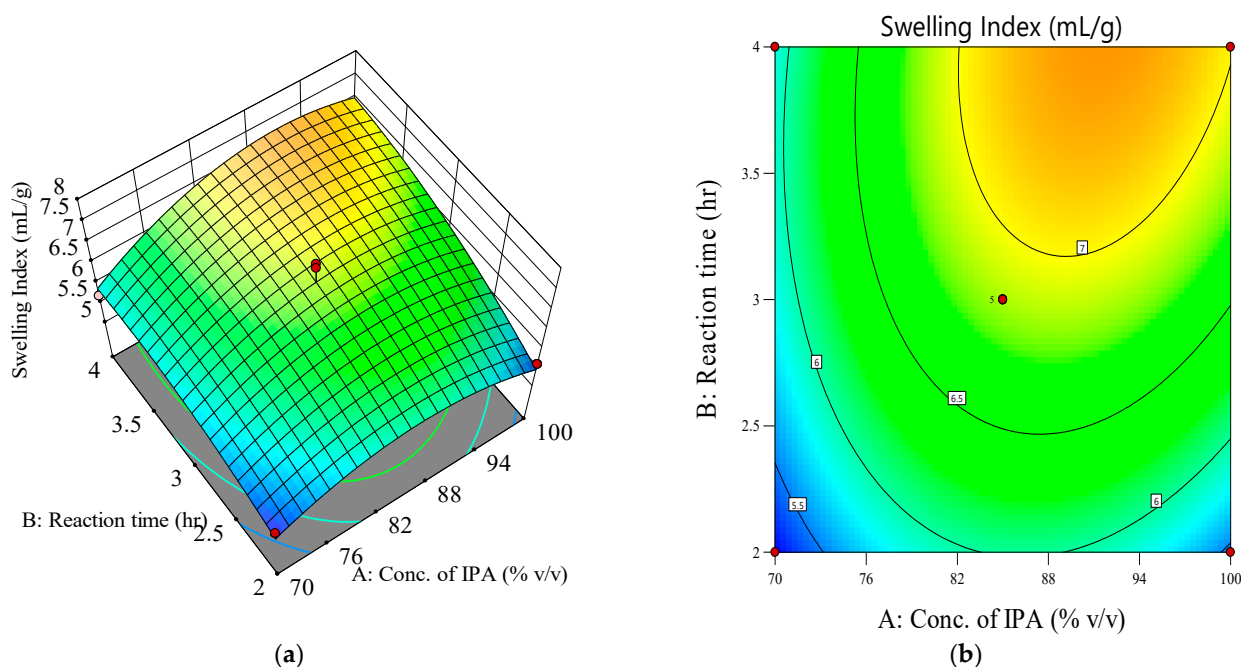


Figure 3. Cont.

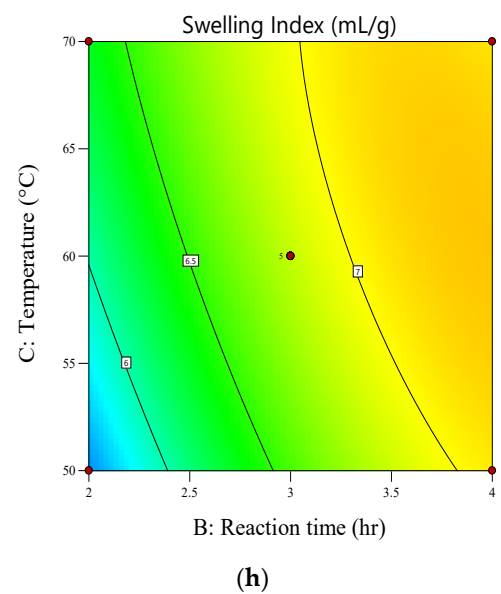
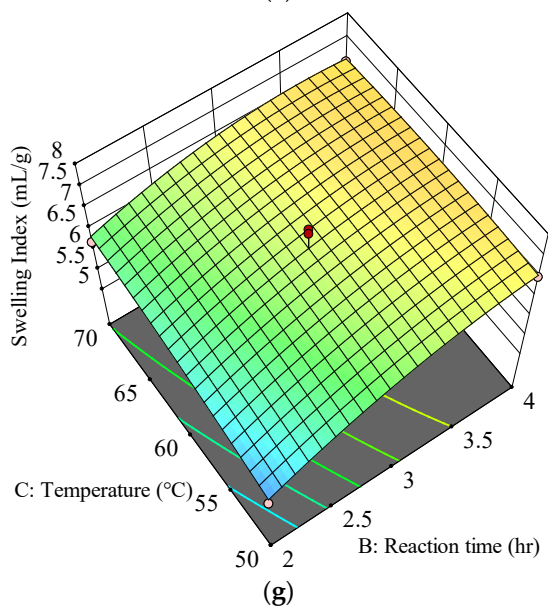
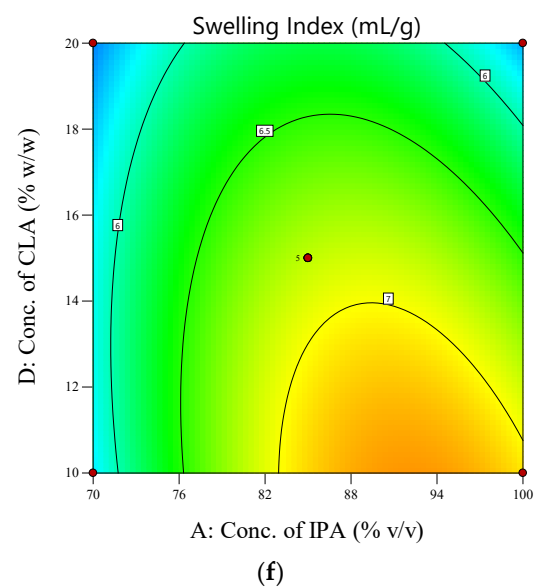
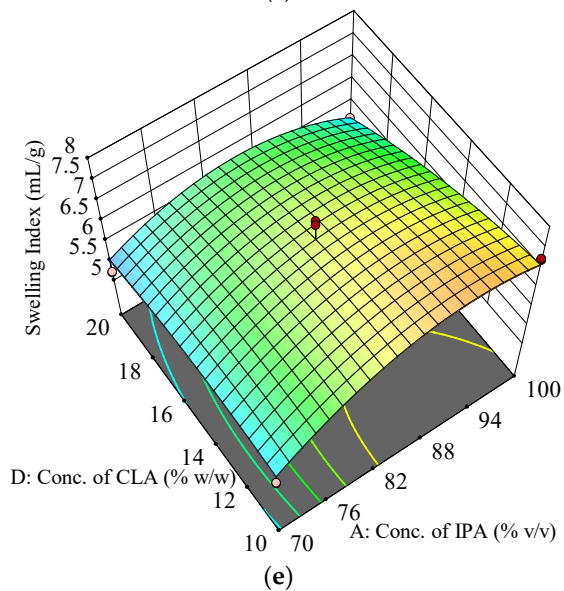
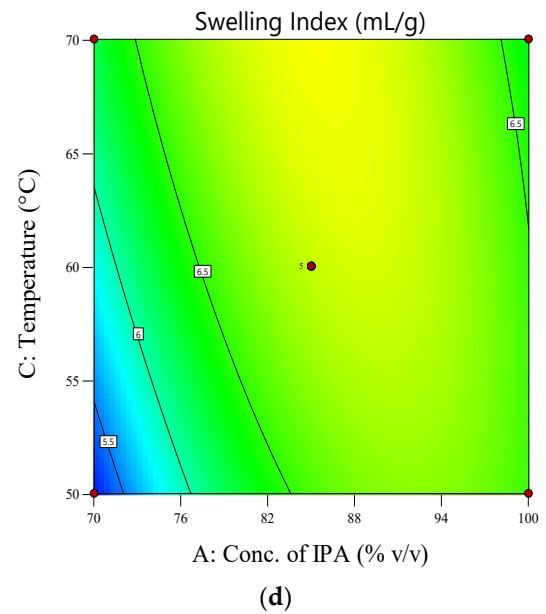
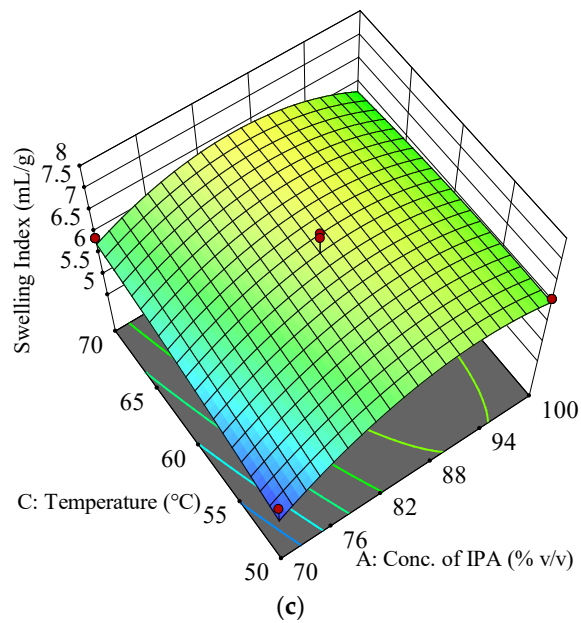
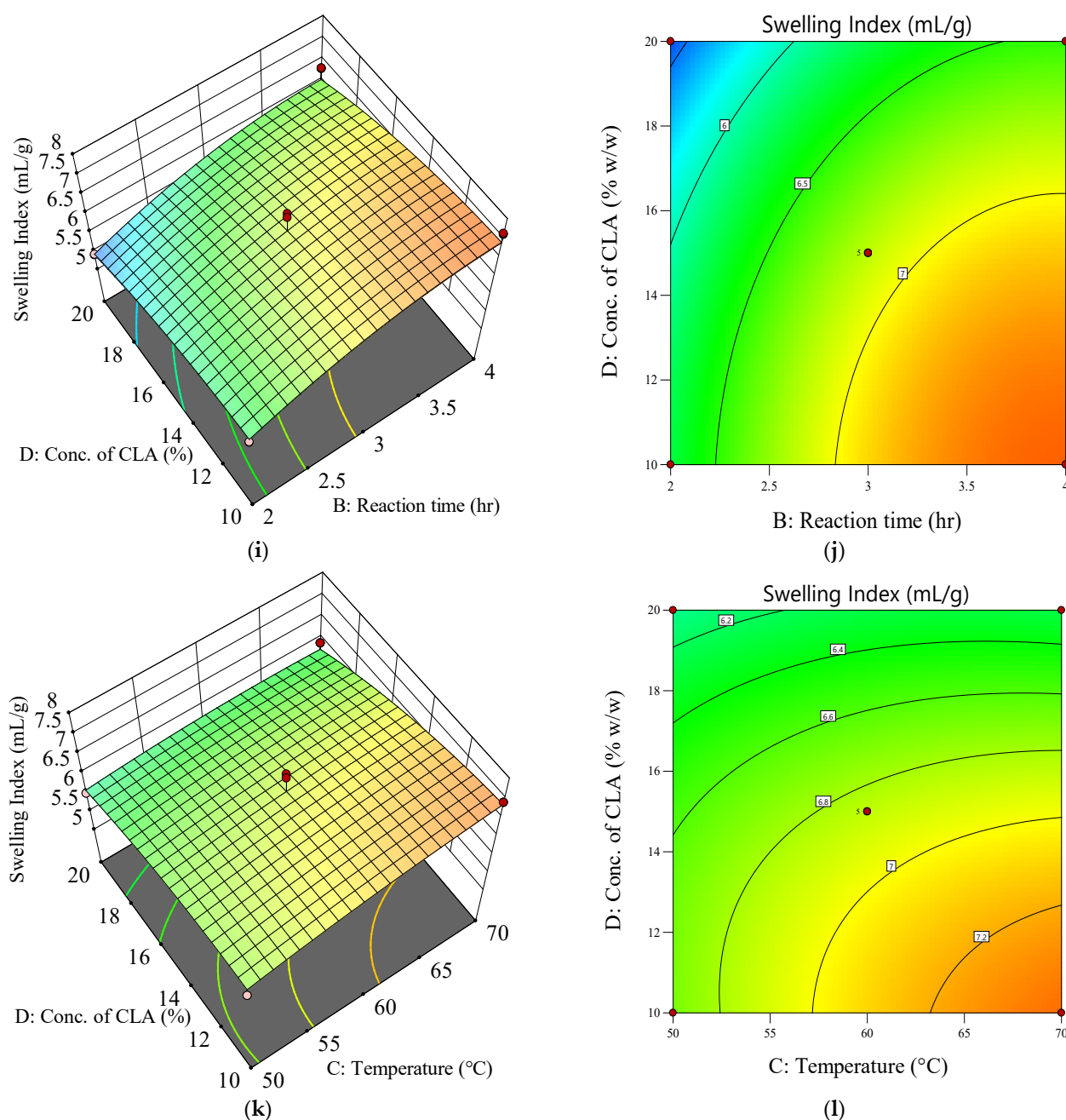


Figure 3. Cont.



**Figure 3.** Three-dimensional response surface and contour plots illustrating the effects of synthesis variables on the swelling index (SI) of synthesized croscarmellose sodium (CCS), (a) 3D response surface showing the interaction between IPA concentration and reaction time; (b) corresponding contour plot; (c) 3D response surface showing the interaction between IPA concentration and reaction temperature; (d) corresponding contour plot; (e) 3D response surface showing the interaction between IPA concentration and CLA concentration; (f) corresponding contour plot; (g) 3D response surface showing the interaction between reaction time and reaction temperature; (h) corresponding contour plot; (i) 3D response surface showing the interaction between reaction time and CLA concentration; (j) corresponding contour plot; (k) 3D response surface showing the interaction between reaction temperature and CLA concentration; and (l) corresponding contour plot.

#### Effects of IPA Concentration and Reaction Temperature on Swelling Index

A gradual increase in the swelling index with increasing temperature, particularly at intermediate IPA concentrations, is demonstrated in Figure 3c. The contour plot dis-

plays moderately elliptical contours (Figure 3d), suggesting a noticeable but less intense interaction compared to the IPA and reaction time effect.

#### Effects of IPA and CLA (Glycolic Acid) Concentration on Swelling Index

In Figure 3e, a distinct dome-shaped surface can be observed, indicating a strong quadratic influence of the CLA concentration. The swelling index increased at lower CLA levels but declined at higher concentrations regardless of IPA concentration. The contour plot confirms this effect through closed, concentric contours (Figure 3f).

#### Effects of Reaction Time and Temperature on Swelling Index

In Figure 3g, the surface plot shows a synergistic effect where the swelling index increases with increases in both the reaction time and temperature up to an optimal region. The contours are slightly elliptical, indicating moderate interaction (Figure 3h).

#### Effects of Reaction Time and CLA (Glycolic Acid) Concentration on Swelling Index

Swelling index increased with reaction time at lower CLA concentrations, while higher CLA levels resulted in reduced swelling, even at extended reaction times (Figure 3i). The contour plot supports this by showing elongated contours, reflecting a significant interaction, as shown in Figure 3j.

#### Effects of Reaction Temperature and CLA (Glycolic Acid) Concentration on Swelling Index

The surface plot indicates that temperature had a positive effect on the swelling index at lower CLA concentrations, whereas at higher CLA levels, temperature changes exerted minimal influence (Figure 3k). The contour plot shows nearly circular contours, implying that this interaction was comparatively weaker (Figure 3l). This confirms that the CLA concentration is the dominant factor governing swelling behavior in this interaction pair.

### 3.6.2. Evaluation of Effects of Multiple Factors on Water Retention Capacity by 3D Surface and Contour Plots

#### Effects of IPA Concentration and Reaction Time on Water Retention Capacity

As shown in Figure 4a, the response surface shows a steady increase in water retention capacity with increasing reaction time across all IPA concentrations. The contour plot displays almost parallel contour lines, indicating minimal interaction between these variables (Figure 4b). Reaction time emerged as the dominant factor influencing water retention capacity, while IPA concentration showed a comparatively weaker effect.

#### Effects of IPA Concentration and Reaction Temperature on Water Retention Capacity

A moderate increase in water retention capacity with rising temperature particularly at higher IPA concentrations can be seen in Figure 4c. The contour plot exhibits gently curved contours, suggesting a mild interaction (Figure 4d).

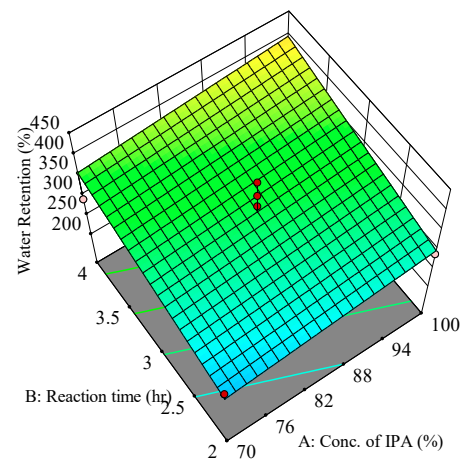
#### Effects of IPA and CLA (Glycolic Acid) Concentration on Water Retention Capacity

Water retention capacity decreased slightly with increasing CLA concentration at all IPA levels (Figure 4e). The surface plot slopes downward along the CLA axis, and the contour plot displays near-linear contours in Figure 4f, indicating that the interaction effect was minimal. Higher CLA levels reduced free hydrophilic sites, thereby lowering the water retention capacity.

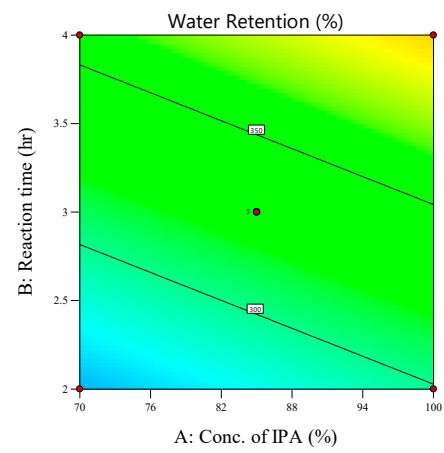
Design Points:

● Above Surface  
○ Below Surface

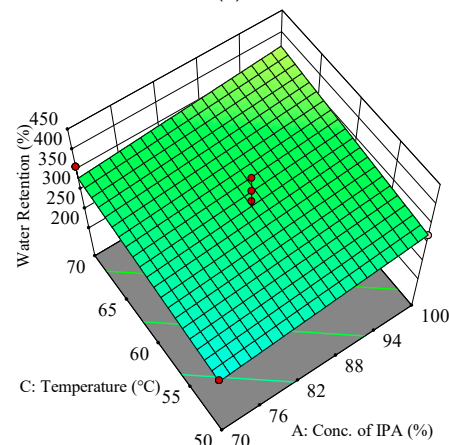
221.006  443.853



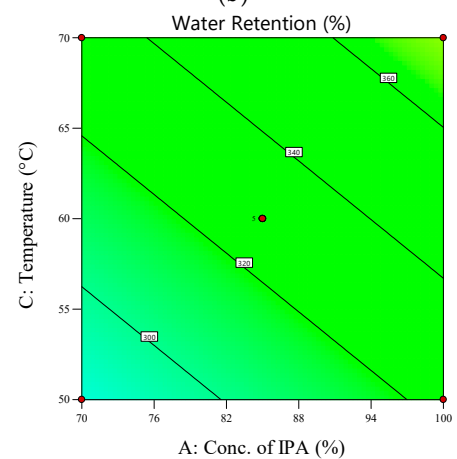
(a)



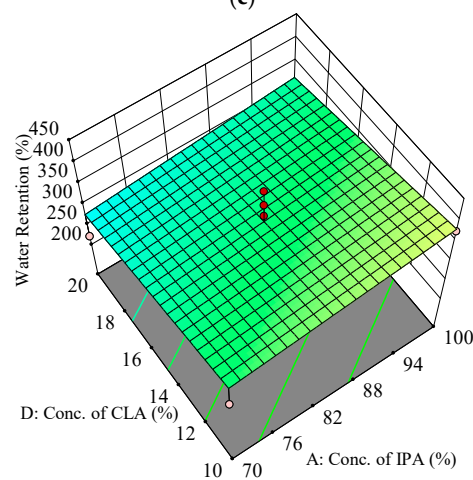
(b)



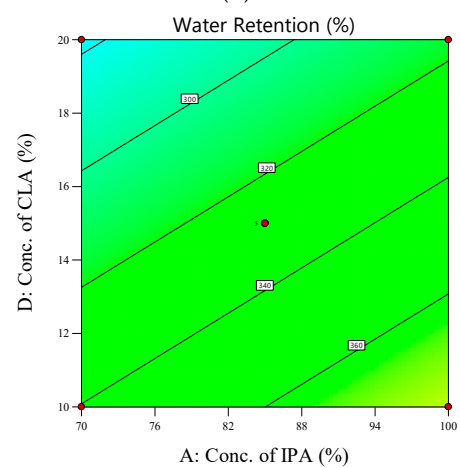
(c)



(d)

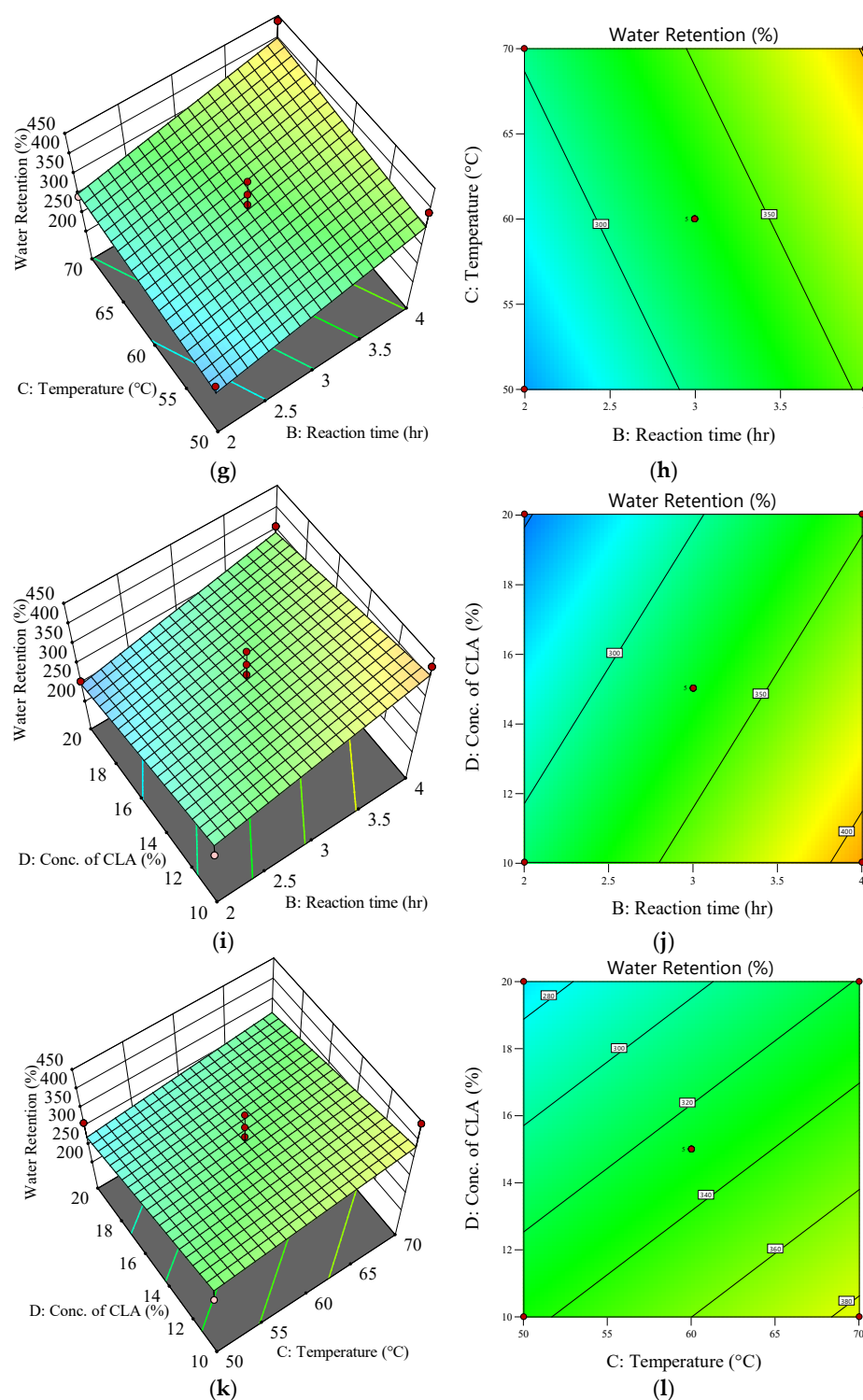


(e)



(f)

Figure 4. Cont.



**Figure 4.** Three-dimensional response surface and contour plots illustrating the effects of synthesis variables on the water retention capacity of synthesized croscarmellose sodium (CCS), (a) 3D response surface showing the interaction between IPA concentration and reaction time; (b) corresponding contour plot; (c) 3D response surface showing the interaction between IPA concentration and reaction temperature; (d) corresponding contour plot; (e) 3D response surface showing the interaction between IPA concentration and CLA concentration; (f) corresponding contour plot; (g) 3D response surface showing the interaction between reaction time and reaction temperature; (h) corresponding contour plot; (i) 3D response surface showing the interaction between reaction time and CLA concentration; (j) corresponding contour plot; (k) 3D response surface showing the interaction between reaction temperature and CLA concentration; and (l) corresponding contour plot.

### Effects of Reaction Time and Temperature on Water Retention Capacity

In Figure 4g, a positive synergistic effect can be observed, where water retention capacity increased with both increasing reaction time and temperature. The contour plot shows moderately curved contours, reflecting a moderate interaction (Figure 4h). Extended reaction time and higher temperature facilitated better polymer network formation, enhancing the water retention capacity.

### Effects of Reaction Time and CLA (Glycolic Acid) Concentration on Water Retention Capacity

The surface plot demonstrates in Figure 4i that reaction time positively affected the water retention capacity at lower CLA concentrations, whereas at higher CLA levels, this effect was diminished. The contour plot also confirms the same pattern (Figure 4j).

### Effects of Reaction Temperature and CLA (Glycolic Acid) Concentration on Water Retention Capacity

As shown in Figure 4k, the response surface indicates a slight increase in water retention capacity with temperature at lower CLA (glycolic acid) concentrations but a flattened response at higher CLA levels. The contour plot shows widely spaced contours, suggesting a weak interaction (Figure 4l). This confirms that the CLA concentration predominantly governs the water retention capacity in this interaction.

### 3.7. Predicted vs. Actual Plot

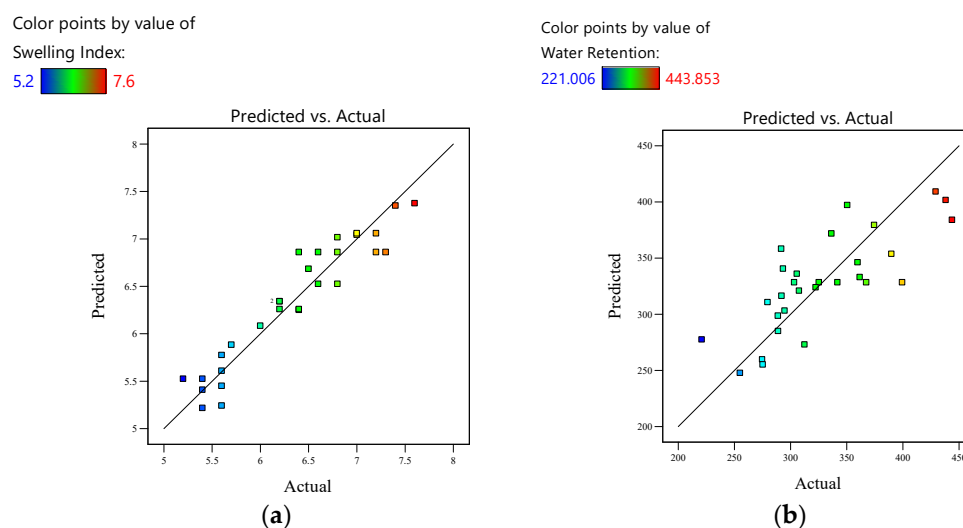
The predicted versus actual plot illustrates assessment of the agreement between experimentally observed response values and those predicted by the developed model. The data points are densely packed along the diagonal line in Figure 5a, indicating excellent agreement between the predicted and actual values. Most data points are distributed near the line of perfect agreement, with only minor deviations, demonstrating that the quadratic model accurately describes the experimental data within the investigated design space. This implies that within the examined design space, the model provides good predictive accuracy for the swelling index. There was no significant bias because there were no substantial systematic variations. The responses were neither regularly overestimated nor underestimated by the model. The model effectively reflected the trend and variability of the swelling index, as evidenced by the smooth transition of the points from low to high values. Figure 5b illustrates the predicted vs. actual plot for water retention capacity, demonstrating good agreement between the experimental observations and model predictions. A moderate degree of scattering was observed around the diagonal line compared to an ideal plot. The model depicts an overall trend but with slightly reduced precision at certain points. The absence of a clear systematic pattern in the residual spread indicates that the deviations are random rather than structural, and no serious model bias is present [33].

The gradual change in point color reflects the magnitude of the response values across the experimental range. These findings are consistent with the ANOVA results and confirm that the developed models provide satisfactory predictive performance for both response variables within the selected experimental region.

### 3.8. Optimization of Reaction Condition

Numerical optimization was performed using the optimization module of Design-Expert® software (Version 13, Stat-Ease Inc., Minneapolis, MN, USA) to determine the optimum synthesis conditions for croscarmellose sodium (CCS). The optimization was carried out using the validated response surface models in combination with the desirability function approach, which simultaneously optimizes multiple responses by maximizing the overall desirability. The independent variables, including IPA concentration (A), reaction

time (B), reaction temperature (C), and glycolic acid concentration (D), were constrained within the experimental ranges defined by the Box–Behnken design. The optimization objective was to maximize both the swelling index (SI) and water retention capacity (WRC) while maintaining all synthesis variables within the investigated experimental region.



**Figure 5.** Predicted versus actual plots for (a) swelling index (SI) and (b) water retention capacity (WRC). Each square represents an individual experimental run, while the solid diagonal line indicates perfect agreement between the predicted and experimental values (predicted = actual).

The numerical optimization generated 100 feasible solutions, and the solution with the highest overall desirability (0.985) was selected as the optimum. The predicted optimum synthesis conditions and the corresponding experimental validation results are presented in Table 8. The predicted optimum synthesis conditions were 93.23% (*v/v*) IPA, 4 h reaction time, 70 °C reaction temperature, and 10% (*w/w* of CMC) glycolic acid (CLA). Under these conditions, the model predicted a swelling index of 7.529 mL/g and a water retention capacity of 443.85%.

**Table 8.** Predicted optimum synthesis conditions and experimental validation results for croscarmellose sodium (CCS) obtained using numerical optimization. A, B, C, and D denote the coded levels of isopropyl alcohol (IPA) concentration (*v/v*), reaction time, temperature, and glycolic acid (CLA) concentration (*w/w* of CMC), respectively.

| Variables             |     |       |                          | Swelling Index (mL/g) |            | Water Retention Capacity (%) |           |
|-----------------------|-----|-------|--------------------------|-----------------------|------------|------------------------------|-----------|
| A                     | B   | C     | D                        | Experimental          | Predicted  | Experimental                 | Predicted |
| 93.23% ( <i>v/v</i> ) | 4 h | 70 °C | 10% ( <i>w/w</i> of CMC) | 7.8 ± 0.2 mL/g        | 7.529 mL/g | 461.491 ± 9.564%             | 443.85%   |

The optimum values for reaction time, reaction temperature, and CLA concentration were located at the boundaries of the investigated design space, indicating that the responses improved toward these limits within the selected experimental region. These factor ranges were established based on preliminary experiments and practical process considerations. Extending the reaction time beyond 4 h or the temperature above 70 °C was considered impractical because of increased processing time, energy consumption, and the potential risk of polymer degradation. Similarly, CLA concentrations below 10% may not provide sufficient crosslinking, whereas concentrations above 20% could result in excessive crosslinking, thereby reducing the swelling performance of CCS.

To verify the reliability of the optimization model, a validation experiment was performed under the predicted optimum conditions. The experimentally obtained swelling index and water retention capacity were  $7.8 \pm 0.2$  mL/g and  $461.491 \pm 9.564\%$ , respectively. These values are in good agreement with the model predictions, confirming the adequacy and predictive capability of the developed optimization model for identifying the optimum synthesis conditions of CCS.

#### 4. Conclusions

Croscarmellose sodium (CCS) was successfully synthesized from sodium carboxymethyl cellulose (CMC) using glycolic acid as the crosslinking agent and optimized through Response Surface Methodology (RSM) based on a four-factor, three-level Box–Behnken Design. FT-IR characterization confirmed the successful conversion of CMC into CCS by retaining the characteristic cellulose backbone while exhibiting spectral features associated with crosslinking. The close similarity between the spectra of the synthesized material and the commercial reference CCS further verified the successful formation of the desired product.

The optimization study revealed that reaction time and glycolic acid concentration were the most influential factors affecting both the swelling index (SI) and water retention capacity (WRC). IPA concentration and reaction temperature also contributed significantly to the functional performance of CCS. The quadratic model developed for SI and the linear model established for WRC showed excellent agreement with the experimental results, with both models being highly significant ( $p < 0.0001$ ). Response surface analysis also demonstrated important interactions among the process variables, particularly between IPA concentration and reaction time, emphasizing the need to optimize these parameters simultaneously rather than individually.

Numerical optimization using the desirability function predicted the optimum synthesis conditions to be 93.23% (*v/v*) IPA, a reaction time of 4 h, a reaction temperature of 70 °C, and 10% (*w/w* of CMC) glycolic acid. Under these conditions, the predicted SI and WRC were 7.529 mL/g and 443.85%, respectively. Experimental validation produced values of  $7.8 \pm 0.12$  mL/g for SI and  $464.49 \pm 5.56\%$  for WRC, demonstrating good agreement with the predicted responses and confirming the accuracy and reliability of the optimization model.

In summary, the RSM-based Box–Behnken Design proved to be an effective and statistically robust approach for optimizing CCS synthesis while reducing the number of experimental trials. The optimized CCS exhibited high swelling ability and excellent water retention capacity, properties that are desirable for its application as a pharmaceutical superdisintegrant in immediate-release tablet formulations. The optimization strategy and predictive models presented in this study may also serve as a practical basis for future process optimization, scale-up, and the development of cellulose-based pharmaceutical excipients.

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