ORIGINAL ARTICLE

Wet heat energy for reaction of 2-hydroxy-1,2,3-propanetricarboxylic acid with caruba and applications for pharmaceutical dosage forms

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ABSTRACT

The reaction of 2-hydroxy-1,2,3-propanetricarboxylic acid (2HT) with caruba (Cb) produces poly-2-hydroxy-1,2,3-propanetricarboxylic acid caruba (P-2HTCb). The study aims to determine the effect of temperature and heating time in the P-2HTCb synthesis reaction and to obtain the optimum conditions for P-2HTCb synthesis. Experiments with 2HT (4.76×10^{-2} M), Cb (4.51×10^{-5} M), and hydrochloric acid (0.12 M) were carried out in a two-factorial design. Temperature and heating time were the optimization factors (40°C–60°C) and heating time (30–45 min). P-2HTCb was characterized by universal attenuated total reflectance, proton magnetic resonance (PMR), differential scanning calorimetry, X-ray diffraction, and scanning electron microscope. All P-2HTCb contained C = O ester at approximately 1736 cm^{-1}, swelling index (SI) 20.52%–24.82%, pH 3.64–4.88, yield 33.10%–39.30%, and esterification effectiveness (Ee) 10.83%–12.85%. The optimum PMR doublet peak of P-2HTCb was at δ = 2.878–2.652 ppm, melting temperature 146°C, diffractogram peak at 19.3800°, and a coral-like wavy surface. Increasing melting temperature, increased SI, increased pH, reduced yield, and reduced Ee. Heating time increased SI, decreased pH, reduced yield, and reduced Ee. The combination of both decreased the SI, pH, yield, and Ee. The optimal conditions for the synthesis of P-2HTCb were 55°C for 40 min. P-2HTCb accelerated the flow of microcrystalline cellulose and provided tablet friability of ≤1%.

Key words: Caruba, wet heating, optimization, poly-2-hydroxy-1,2,3-propanetricarboxylic acid caruba, 2-hydroxy-1,2,3-propanetricarboxylic acid

INTRODUCTION

Cb consists of mannohexose and galactohexose (M-G) (4:1)[1-4] with the advantages of being safe, easy to obtain, and affordable,[2,5] often as a binder, disintegrant, drug release negative matrix, suspension agent, gel agent, and others.[6-8] Cb has high viscosity at low concentrations,[9] which causes inhibition of drug release in conventional tablets. Efforts to reduce viscosity by esterifying with 2HT (citric acid) on the C6 of M-G have a high probability of binding to the COOH of 2HT under acidic conditions.[10-14]

Optimization factors according to the factorial design were temperature (40°C–60°C) and heating time (30–45 min)

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using a water bath as the heat source. P-2HTCb was characterized by universal attenuated total reflectance (UATR), proton magnetic resonance (PMR), differential scanning calorimetry (DSC), X-ray diffraction (XRD), scanning electron microscope (SEM), swelling index (SI), pH, yield, and esterification effectiveness (Ee). The experiment aimed to determine the effect of temperature and heating time and to obtain optimal conditions for P-2HTCb synthesis. Optimal water-bath conditions are novel for shortening reaction times and achieving high yields. P-2HTCb's lower viscosity and hydrophilicity expand its potential as a pharmaceutical excipient.

MATERIALS AND METHODS

Materials

Cb (Cargill, France), 2HT (Merck, Germany), hydrochloric acid (HCl) (Sigma Aldrich Chemie, USA), aquades and acetone (Cawan Anugerah Chemika, Indonesia), and microcrystalline cellulose (MC) (Flocel, India).

P-2HTCb synthesis

Cb mucilage 100 mL (4.51×10^{-5} M) was added to 2HT (4.76×10^{-2} M) and HCl (0.12 M), and placed in a water bath [Table 1]. The mucilage was cooled, precipitated, washed with acetone-aquadest (1:1), dried, ground, and characterized.[15-17]

Universal attenuated total reflectance

P-2HTCb was spread on a diamond universal attenuated total reflectance and pressed with a rod (Perkin Elmer Spectrum, USA).[15-17]

Proton magnetic resonance

The P-2HTCb filtrate (12 mg, 500 µL D_2O) in the tube was placed in an NMR holder (JEOL, Japan). P-2HTCb (3.10^{-3} g, 7 µL distilled water).[15-17]

Differential scanning calorimetry

The heating temperature of DSC (Shimadzu, Japan) was increased from 50°C to 250°C to moist P-2HTCb (±3 mg).[17]

X-ray diffraction

P-2HTCb was observed by XRD (Shimadzu, Japan). Cu detector 1.54060A, Scanning 3.0200°–80.0000° (θ–2θ), 4°/min, and DS: 1°; SS: 1°; RS: 0.30 mm.[17]

Scanning electron microscope

P-2HTCb was coated with platinum and observed by SEM (JEOL, Tokyo).[16,17]

Swelling index, pH, yield, and esterification effectiveness

The filter paper has been weighed after it was filled with P-2HTCb powder (25 mg) in a glass funnel and poured with hot distilled water (50 mL). The P-2HTCb mucilage was dried and weighed. The SI (%) of the mucilage weight compared to the weight of the dry powder.[18]

The electrode of a calibrated pH meter (Metrohm Switzerland) was dipped in the P-2HTCb filtrate, and the pH was displayed on the monitor.[19] The yield is the weight of P-2HTCb compared to the total weight of 2HT and Cb. The effectiveness of the P-2HTCb reaction was measured by the potentiometrically (Metrohm, Switzerland) [Table 1].[16,17]

Optimization and statistics

A factorial design with temperature (40°C–60°C) and heating time (30–45 min) as optimization factors was used. The initial conditions were A (40°C, 30 min), B (40°C, 45 min), C (60°C, 30 min), and D (60°C, 45 min). The SI, pH, and yield were analyzed using two-way ANOVA. The

Table 1: Detailed characterization of poly-2-hydroxypropane-1,2,3-tricarboxylic carubin from various reaction conditions

Condition code	Temperature (°C)	Heating time (min)	Wavenumber (cm^{-1})	SI (%)	pH	Yield (%)	Ee (%)
A	40	30	1736.01	20.52±0.29	4.83±0.06	39.30±0.93	12.85±0.10
B	40	45	1735.09	21.48±018	3.64±0.24	38.80±0.60	12.69±0.13
C	60	30	1735.06	24.07±0.31	4.88±0.10	37.15±0.53	12.15±0.10
D	60	45	1735.00	24.82±0.26	3.91±0.08	33.10±0.49	10.83±0.11
O	55	40	1736.06	23.38±0.33	4.18±0.17	36.09±0.23	11.85±0.15

SI: Swelling index

Table 2: Results of the two-way ANOVA analysis

Factor	SI		pH		Yield	
F (df1, df2)	*F* (1.8)	*P* (0.05)	*F* (1.8)	*P* (0.05)	*F* (1.8)	*P* (0.05)
Temperature	554.6792	0.0000	2.1226	0.1832	198.3982	0.0000
Heating time	42.7755	0.0002	165.3504	0.0000	72.1827	0.0000
Interaction	2.6468	0.1424	0.9848	0.3501	35.531	0.0003

SI: Swelling index

experimental values were compared with the predicted values using a *t*-test.

Application of P-2HTCb

P-2HTCb (1.5% and 3%) optimization and statistics as a glidant for MC tablet mass (100 g), pressed into tablets (700 mg) for friability testing (Erweka, Germany).[20,21] Friability is measured from the weight of the lost particles relative to the initial weight.[20,21]

RESULTS AND DISCUSSION

P-2HTCb synthesis

The reaction begins with protonation of O from C = O in 2HT to create C^+. O attacks H^+ from HCl to create $^+$O-H. O-H from C6 in M-G attacks C^+ atom in 2HT so that the C = O double bond is broken to create $(O\text{-}H)_2$ and HCO^+. The OH receives an H donor from HCO^+, producing HOH^+ and C-O from both monomers. H^+ from OH and H_2O^+ is lost. Summary of the reaction, C^+ from C = O in 2HT bonds with O from O-H in M-G [Figure 1].

Universal attenuated total reflectance

Infrared spectra and wave numbers [Table 1 and Figure 2] to identify chemical groups in each condition are 3349.80–3306.07 cm^{-1} (O-H), 2927.60-2853.00 cm^{-1} (C-H), 1736.06–1735.00 cm^{-1} (C = O). These wave numbers are in accordance with previous studies and the identical C = O ester of P-2HTCb.[15-17,22-24]

Proton magnetic resonance

The ^{1}H NMR spectra of 2HT and P-2HTCb in O conditions [Figure 3] show a pair of doublet peaks at δ = 2.878–2.652 ppm identical to the H side of 2HT.[25] The multiplet peak of P-2HTCb at δ = 5.027–3.328 ppm is C-H in M-G. The 2HT doublet peaks shift because the presence of M-G affects proton transfer and loss.[15,16] The ^{1}H NMR spectrum of M-G is shown in Figure 3, as in the previous experiment.[26,27]

Differential scanning calorimetry

The thermogram of P-2HTCb in O conditions [Figure 4a] shows that the change in state of P-2HTCb is influenced by

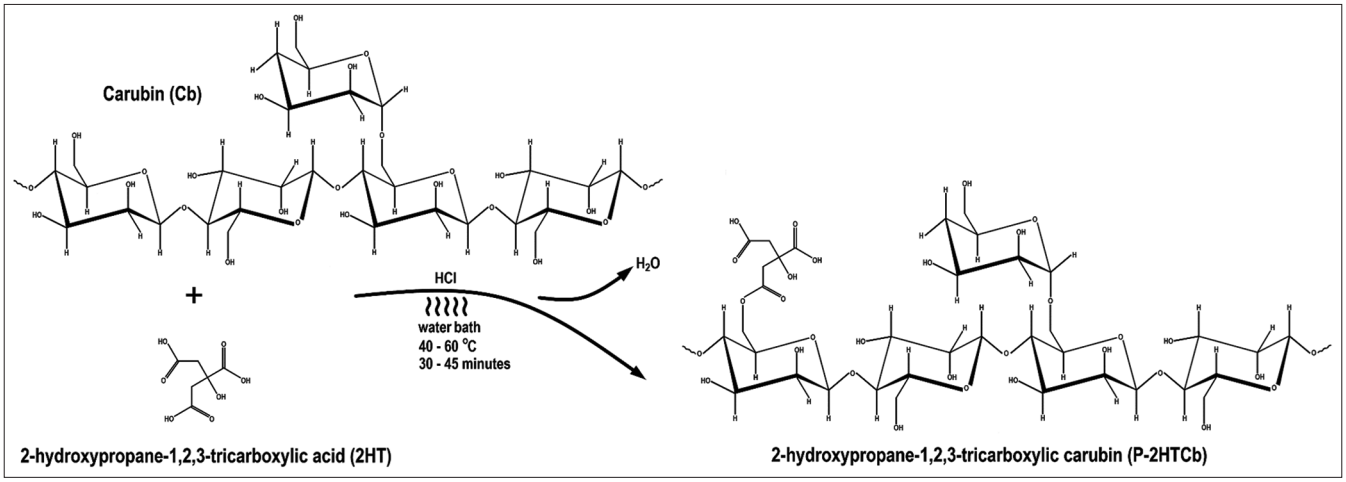

Figure 1: Reaction mechanism for the synthesis of P-2HTCb

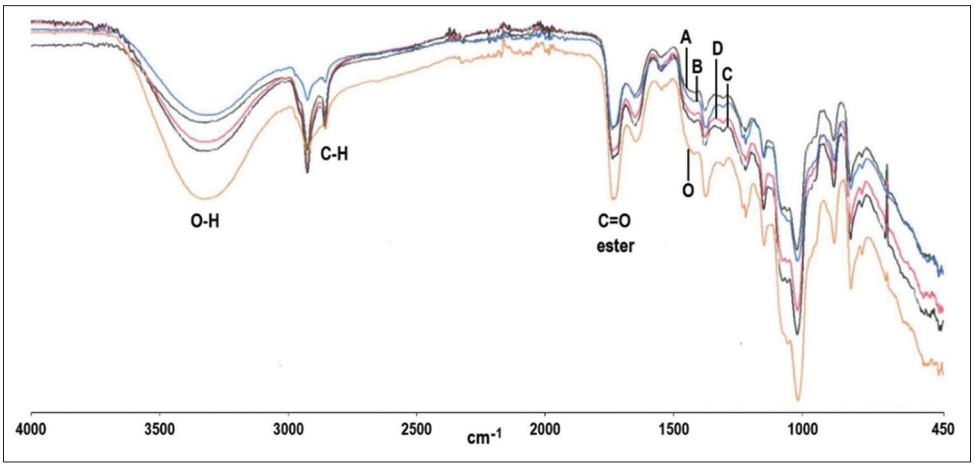

Figure 2: Infrared spectra of P-2HTCb from synthesis conditions: A (40°C, 30 min), B (40°C, 45 min), C (60°C, 30 min), D (60°C, 45 min), and O (55°C, 40 min)

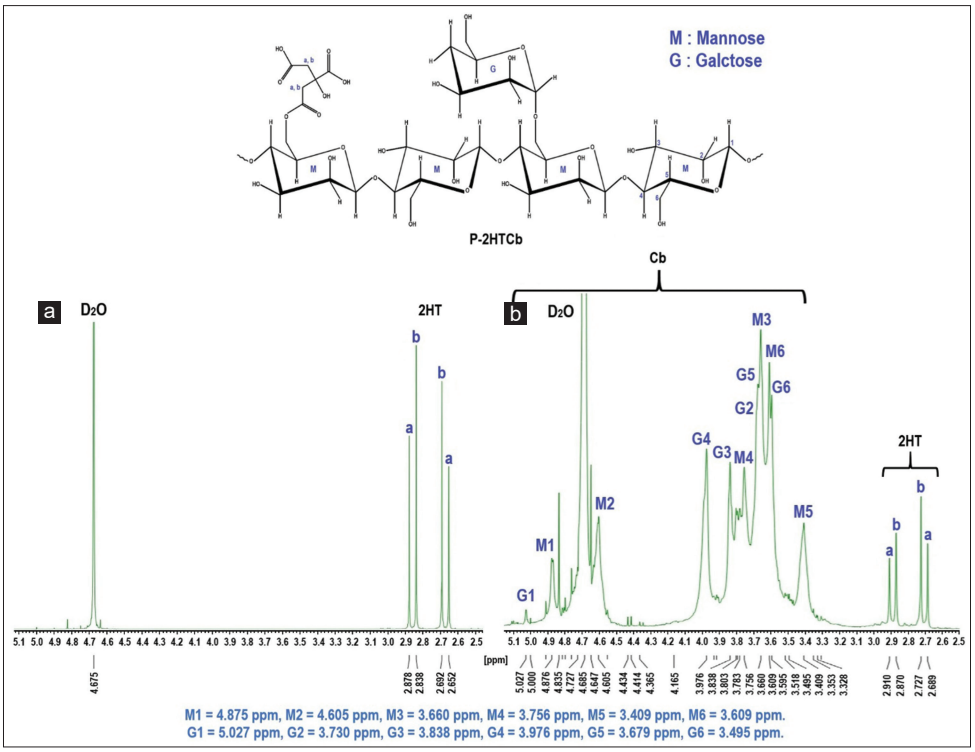

Figure 3: ^{1}H NMR spectra of 2HT (a) and P-2HTCb (b) from optimum conditions (O) (55°C, 40 min)

an increase in the endothermic enthalpy temperature (ΔH) of 3.30 kJ/g. P-2HTCb is moist, begins to change at 137.33°C (Tg), melts completely at 146.32°C (Tm), and crystallizes at 159.25°C (Tc). These results are in accordance with previous experiments and indicate successful esterification.[17] The ΔH value of P-2HTCb is lower than that of Cb (6.70 kJ/g), so that P-2HTCb is more hydrophobic and traps solvents less well than Cb.

X-ray diffraction

The diffractogram of P-2HTCb in O conditions [Figure 4c] shows it as an irregular, amorphous molecule. The diffractogram peak (19.3800°) is consistent with previous studies.[17] P-2HTCb is amorphous due to the influence of M-G molecules form Cb, including galactomannan.[28]

Scanning electron microscope

The surface morphology of P-2HTCb from O condition (×3500) [Figure 4b] is wavy like coral according to the wavy Cb character and coral according to the 2HT character.

Swelling index, pH, yield, and esterification effectiveness

The results of the SI, pH, yield, and Ee are presented in Table 1. The Ee profile is similar to the yield profile. SI (Equations 1 and Figure 5a), pH (Equations 2 and Figure 5b), and yield (Equations 3 and Figure 5c) are the results of Design Expert, where the optimization response (Y), temperature (A), heating time (B), and the combination of both (AB) are presented.

$$Y = 22.720 + 1.720A + 0.430B - 0.053AB \quad (1)$$

$$Y = 4.310 + 0.080A - 0.540B + 0.055AB \quad (2)$$

$$Y = 37.090 - 1.960A - 1.140B - 0.890AB \quad (3)$$

The coefficients of the three equations indicate that temperature increases the SI (0.430) but decreases pH (−0.540) and yield (−1.140). The combination of both decreases the SI and yield but increases pH.

Temperature energizes the reaction between the C^{+} of 2HT and the O of the O-H of M-G. High temperatures provide more reaction opportunities and a faster reaction rate for the C^{+} of 2HT with the O of the O-H of M-G. Multiple bonds are formed, increasing the swelling arrest capability. Temperature also risks breaking the P-2HTCb bond, causing an increase in the pH of P-2HTCb and a decrease in yield due to leaching.

Long heating times increase the SI by creating strong bonds between the C^{+} of 2HT and the O of the O-H of M-G. P-2HTCb with a high 2HT content lowers the pH. As new bonds form, P-2HTCb breaks down due to prolonged exposure to high temperatures. Under these conditions, the yield of P-2HTCb decreases.

The combination of the two decreases the SI and yield because high temperatures and prolonged

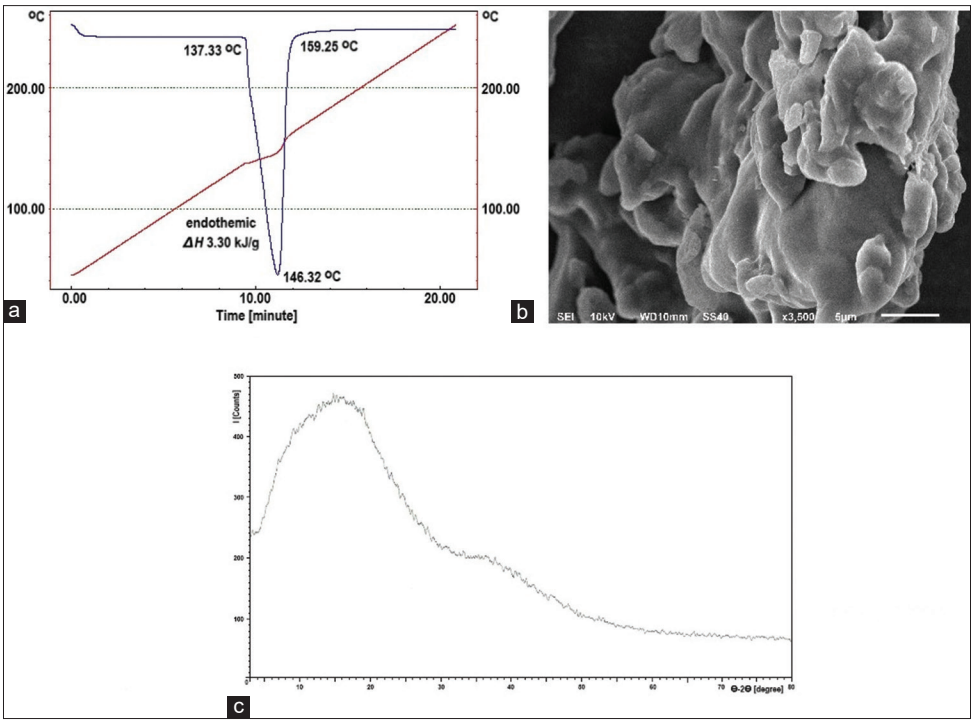

Figure 4: Differential scanning calorimetry thermogram (a), scanning electron microscope images (b), and X-ray diffraction diffractogram (c) of the P-2HTCb from optimum condition (O)

Table 3: Tablet and tablet mass evaluation results

Glidant	Concentration (%)	Flow time (s)	Angle of repose (°)	Friability (%)
P-2HTCb	1.5	7.67±0.12	34.15±0.14	0.30±0.01
	3.0	6.70±0.20	33.11±0.16	0.28±0.01
Talc	1.5	9.37±0.15	36.85±0.16	0.29±0.02
	3.0	13.10±0.20	35.09±0.11	0.26±0.02
Control	-	18.57±0.15	39.45±0.25	-

P-2HTCb: Poly-2-hydroxypropane-1,2,3-tricarboxylic carubin

exposure break down the P-2HTCb bond, decomposing into 2HT and Cb derivatives, which increase the pH.

Optimization and statistics

Prediction and overlap plot through Design Expert [Figure 5d] with the results of heating temperature 55°C for 40 min (condition O). ANOVA of the influence of factors is presented in Table 2. The predicted values for each response are SI 23.39%, pH 4.24, and yield 36.03%, which are further verified through synthesis experiments. A *t*-test was performed on the predicted response value with the experimental response value. The results of the *t*-test indicate that the $\bar{x} = 2.38 \pm 0.33$ t (2) = 0.0697, $P = 0.4739$ (SI); $\bar{x} = 4.18 \pm 0.17$ t (2) = 0.6178, $P = 0.2851$ (pH); $\bar{x} = 36.09 \pm 0.23$ t (2) = 0.0251, $P = 0.4906$ (Yield), indicating that there is no significant difference ($t < 4.3027$) between the values.

Application of P-2HTCb

The results of the flowability evaluation [Table 3] show that the glidant accelerates the flow of MC by filling pores and smoothing the walls of MC particles, making them slippery and easier to move. The friability of the tablet with the glidant shows brittleness <1%. P-2HTCb on the tablet surface is mobile, so it is released when there is movement.

CONCLUSION

Temperature increases the SI, increases pH, and reduces yield. Heating time increases the SI, decreases pH, and decreases yield. The combination of temperature and heating time decreases the SI, pH, and yield. The optimal condition for the synthesis of P-2HTCb was 55°C for 40 min. P-2HTCb increased MC flow and provided tablet friability ≤1%.

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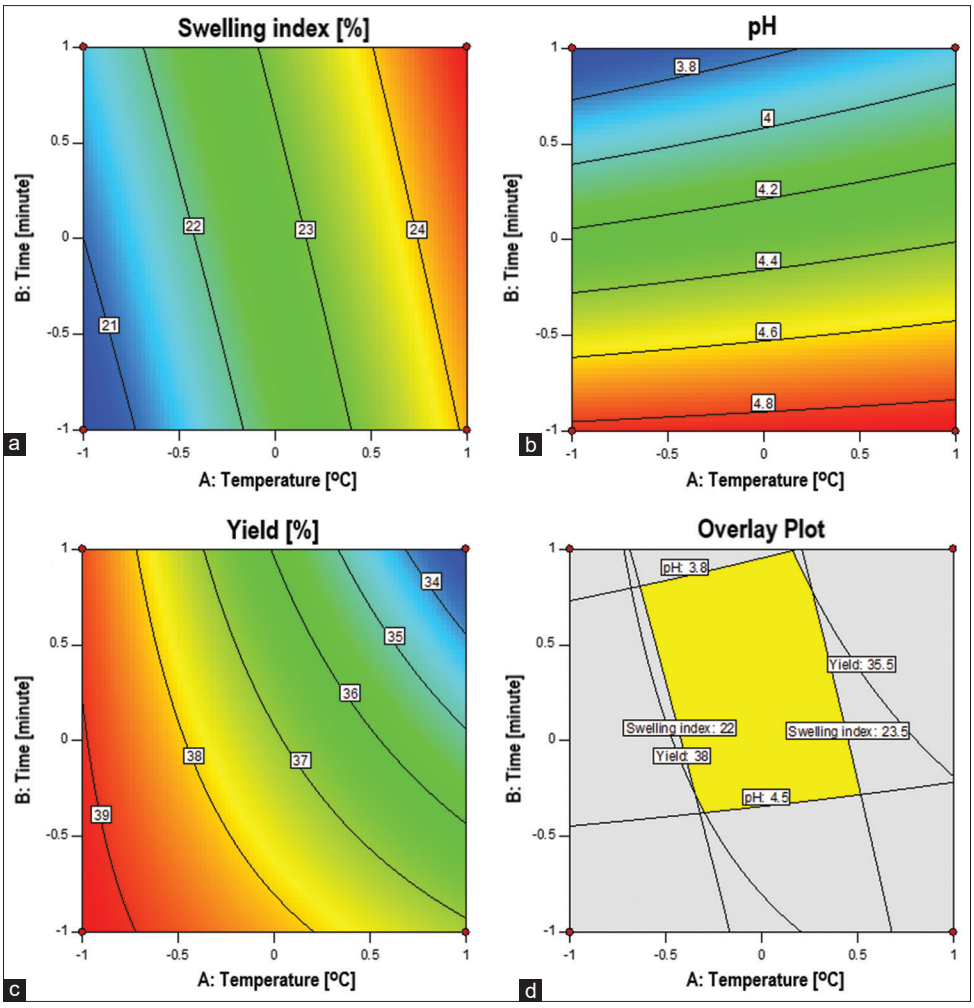

Figure 5: Counter and overlay plot: (a) swelling index, (b) pH, (c) yield, and (d) overlay

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Nil.

Conflicts of interest

There are no conflicts of interest.

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