GREEN SYNTHESIS AND ISOCONVERSIONAL THERMAL ANALYSIS OF HPMC ACETATE: A POTENT MATRIX FOR DRUG DELIVERY

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An efficient, green and commercially viable method for acetylation of cellulose ethers has been developed using acetic anhydride activated with iodine. Iodine was dissolved in acetic anhydride followed by the addition of commercially important cellulose ether, *i.e*., hydroxypropylmethylcellulose (HPMC) and reaction proceeded under solvent-free conditions for 3 h at 50 °C. HPMC acetates were efficiently synthesized, purified and characterized. These HPMC acetates were found soluble in different organic solvents. Under solvent-free conditions, HPMC acetate was synthesized with a DS of 2.53. Highly functionalized HPMC acetate was characterized by FTIR and ^{1}H NMR spectroscopic techniques. Thermal analysis and kinetics have revealed higher thermal stability imparted to HPMC after acetylation. The Flynn-Wall-Ozawa (FWO) isoconversional method was applied for kinetic studies and the energy of activation (*Ea*) value for HPMC acetates was found to be 71.07 kJ/mol, higher than that for unmodified HPMC. Thermodynamic parameters (ΔH^*, ΔG^* and ΔS^*) are also reported. Thermal stability was compared in terms of integral procedural decomposition temperature (IPDT) and comprehensive index of intrinsic thermal stability (ITS) using Doyle's method. The IPDT values for HPMC and HPMC acetates were found to be 354 and 362 °C, respectively, confirming higher thermal stability of HPMC acetate as compared to HPMC.

Keywords: acetylation, acetic anhydride, esterification, hydroxypropylmethylcellulose, iodine, isoconversional thermal analysis

INTRODUCTION

Mixed cellulose ether esters (MCEE) are famous inactive pharmaceutical ingredients in different formulations of drugs.[1] Cellulose ethers, particularly, HPMC and hydroxypropylcellulose (HPC), have enormous applications in daily life, pharmaceutical and medicinal fields.[2-4] MCEE are also of high importance in the fields of drug recrystallization[5,6] and formulation design.[7]

MCEE are prepared by reacting cellulose ethers with different acetylating reagents.[8] Hence, chemical modification of HPMC to form HPMC acetates may be performed as with cellulose and HPC.[9-11] Literature has indicated a number of methods for acetylation of polysaccharides, which include the use of acetyl chloride with pyridine,[12] acetic anhydride with pyridine or 4-dimethylaminopyridine[13] and acetic anhydride activated with strong acids or metallic catalysts.[14,15] Likewise, homogeneous acetylation reactions use different solvents, which need to be removed from the product, hence require extra necessary work-up procedure. The aforesaid methods use expensive, toxic and environment-hostile reagents, hence it is necessary to develop the environment-friendly and cost-effective acetylation procedures. Iodine is environment-friendly, commercially available, cheap and powerful anhydrides activating agent. Therefore, catalytic applications of iodine for acetylation using acetic anhydride are nowadays being explored extensively on small organic molecules,[16,17] as well as on polysaccharides.[18,19]

Herein, we are reporting on the isoconversional thermal analysis of commercially important and highly functionalized HPMC acetate (*i.e*., MCEE) and its comparison with unmodified HPMC. Our aim is to exploit the worth of an efficient and mild method that uses acetic anhydride activated with iodine.

EXPERIMENTAL

Materials

Hydroxypropylmethylcellulose (HPMC-E5, USP 26) was obtained from Zhejiang Zhongbao Imp. & Exp. Corp., Ltd., China. HPMC product specification indicated that it contains hydroxypropyl moiety (7.5%), O-methyl groups (28%) and the rest are the free hydroxyls (64.5%). Before subjecting to the acetylation reaction, HPMC was dried under vacuum at 110 °C for 2 h. Acetic anhydride, iodine and analytical grade organic solvents (Fluka) were used as procured.

Measurements

FTIR (KBr pellet) spectra of HPMC and HPMC acetates were recorded on a Prestige-21 (Shimadzu, Japan) instrument. The KBr pellets of samples were dried before analyses to remove moisture traces. ^{1}H NMR (400 MHz, NS 32, 40 °C) spectra of HPMC in D_2O and HPMC acetate in $CDCl_3$ were acquired on a Bruker NMR machine. For comparative thermal response, thermal analysis of HPMC and HPMC acetate was performed on a SDT Q 600 (TA Instruments, USA) thermal analyzer. The studies were performed at the onset of significant weight loss from the heated sample under nitrogen at heating rates of 5, 10, 15 and 20 °C/min from ambient temperature to 800 °C.

Acetylation of HPMC

Iodine (0.5 g, 3.9 mmol) was mixed with acetic anhydride (8 mL, 84 mmol) and stirred for 15 min under solvent-free conditions. Pre-dried HPMC (2.0 g, 8.76 mmol) was added to the above iodine-activated acetic anhydride solution and the resulting mixture was further heated at 50 °C for 3 h. A saturated aq. sodium thiosulphate solution was freshly prepared and added dropwise to the reaction mixture in order to remove excess of iodine (catalyst). This work-up ended with the formation of precipitates of HPMC acetate. The product was then washed thrice by chilled water, further purified by re-precipitation from acetone into water and then again washed thrice. The precipitates of HPMC acetate were vacuum-dried at 50 °C.

Yield: 3.5 g (82%); DS (degree of substitution): 2.53; FTIR (KBr, cm^{-1}): 3483 (O-H), 2927 (C-H), 1747 (C=O), 1456 (CH), 1057 (C-O-C); ^{1}H-NMR (400 MHz, $CDCl_3$, δ ppm): 2.89-5.04 (HPMC repeating unit-H-1-8, 10); 1.13 (H-9); 2.09 (H-11).

Calculations of DS

For the purpose of calculating the DS, a sample (100 mg) was dissolved in 0.1N aq. NaOH (100 mL) and the solution was stirred for 24 h at ambient temperature. Then, the DS of acetylation onto HPMC was calculated using standard acid base titration, as opted in a reference.[19]

Thermal analysis and degradation kinetics

Isoconversional thermogravimetric analyses of HPMC and HPMC acetates were performed on a TA Instruments SDT-Q600 Simultaneous TGA/DSC thermal analyzer. Thermal degradations of the samples were investigated at multiple heating rates (5, 10, 15 and 20 °C/min) under nitrogen atmosphere purging at 150 mL/min flow rate.

The most common approach in the thermal analysis of materials is to study the thermal degradation behavior in terms of degradation temperatures accompanied with weight loss and char yield, then the kinetic parameters of these thermal degradations are investigated. The initial temperature of degradation (Tdi), temperature of maximum loss (Tdm) and final temperature of degradation (Tdf) of HPMC and HPMC acetates were noted from the respective TG curves acquired at four different heating rates. Different kinetic parameters, *i.e.*, energy of activation (*Ea*) and frequency factor (*A*), are calculated using various differential or integral methods. All these methods are derived from the Arrhenius equation (Eq. 1):

$$\frac{d\alpha}{dt} = Ae^{-\frac{Ea}{RT}}(1-\alpha)^n \qquad (1)$$

where α is the conversion rate, *Ea* is the apparent kinetic energy of the degradation reaction, *A* is the frequency factor, *n* is order of reaction, *R* is the gas constant, and *T* is the absolute temperature. In TGA, the conversion extent (α) of a degradation reaction is calculated using the following expression (Eq. 2):

$$\alpha = \frac{M_0 - M_t}{M_0 - M_\infty} \qquad (2)$$

where M_0 and M_∞ represent the initial and final mass of the sample. M_t is the mass of the sample at any value of temperature. Ozawa, Flynn and coworkers[20,21] modified the Arrhenius equation and developed an integral method to calculate *Ea* of thermal degradation reactions. The mathematical form of their method is given below (Eq. 3):

$$\log\beta \cong 0.457\left(-\frac{Ea}{RT}\right) + \left[\log\left(\frac{AEa}{R}\right) - \log F(\alpha) - 2.315\right] \qquad (3)$$

where β is the heating rate.

Thus, at the same conversion, the activation energy, *Ea*, is obtained from the straight graph, which is plotted between log β and 1000/*T*.

The values for reaction orders (*n*) were calculated from the shape indices of the 2nd derivative thermogravimetric (2DTG) curves using Kissinger's method,[22] as given below (Eq. 4):

$$S = \frac{\left|\frac{d^2\alpha}{dt^2}\right|_L}{\left|\frac{d^2\alpha}{dt^2}\right|_R} \quad (4)$$

where the subscripts *L* and *R* indicate left and right ($d^2\alpha/dt^2$) values of the peak on 2DTG curves. The value of *n* can be calculated from the shape index (*S*) value using the following expressions (Eqs. 5 and 6):

$$n = 1.88S \quad (S \geq 0.45) \quad (5)$$

$$n = 1.26S^{0.5} \quad (S \leq 0.45) \quad (6)$$

The integral procedural decomposition temperature (IPDT) and the comprehensive index of intrinsic thermal stability (ITS), which complete the shape of the TG curve, were calculated by the method proposed by Doyle.[23] Since most of the degradation products of polymers are gaseous (CO_2 and H_2O) in nature and IPDT implicates the volatile parts of the polymers, so it reveals the inherent thermal stability of the polymeric materials.[24,25] ITS and IPDT values of HPMC and HPMC acetates were calculated for all TG curves acquired at various heating rates and their mean values are reported.

The thermodynamic parameters, such as change in entropy (ΔS^*), enthalpy (ΔH^*), and change in Gibbs free energy (ΔG^*), were also determined according to the method reported by Eyring and Polanyi.[26] All thermal data were evaluated by using Universal Analysis 2000 software, version 4.2E (TA Instruments, USA), and MS Excel®2010.

RESULTS AND DISCUSSION

Green synthesis of HPMC acetate

Besides the catalytic profile of iodine,[27,28] it has attracted the attention of the researchers working on polysaccharide modification, particularly acetylation, because it activates carboxylic acid anhydrides. Keeping in view the efficiency of the iodine as an environment-friendly catalyst for acetylation of alcohol under solvent-free conditions,[16,18] HPMC acetates were synthesized using acetic anhydrides activated with iodine using moderate temperature (50 °C) and shorter time (3 h) under solvent-free conditions (Table 1). The product obtained was soluble in different organic solvents.

FTIR spectroscopic analysis

FTIR (KBr) spectrum of HPMC acetate **3** showed a distinct ester peak at 1747 cm^{-1}, indicating the extent of acetylation. The spectra of HPMC and HPMC acetate shown in Fig. 1 are self-explanatory. The spectrum of HPMC acetate displayed a weaker signal for still free OH absorption at 3483 cm^{-1}. The presence of all vital absorptions of ester carbonyl and polymer backbone in the spectra indicated the success of the acetylation reaction.

Table 1
Reactions and conditions for the synthesis of HPMC acetates

Sample	Mole ratio	Yield (%)	Degree of substitution	Solubility
1	1:1.5	78	1.19	DMA, DMSO
2	1:3	85	2.12	DMA, DMSO
3	1:6	82	2.53	DMSO, $CHCl_3$

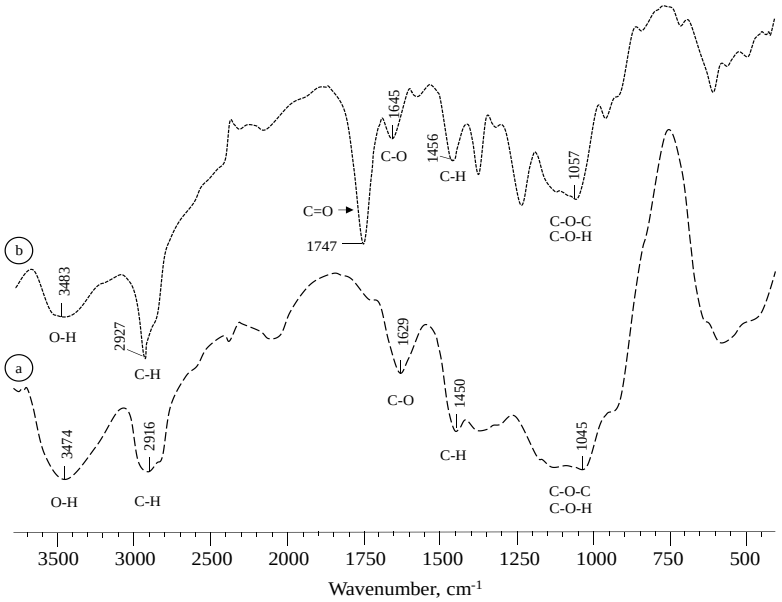

Figure 1: FTIR (KBr) spectra of pure HPMC (a) and acetylated HPMC (b)

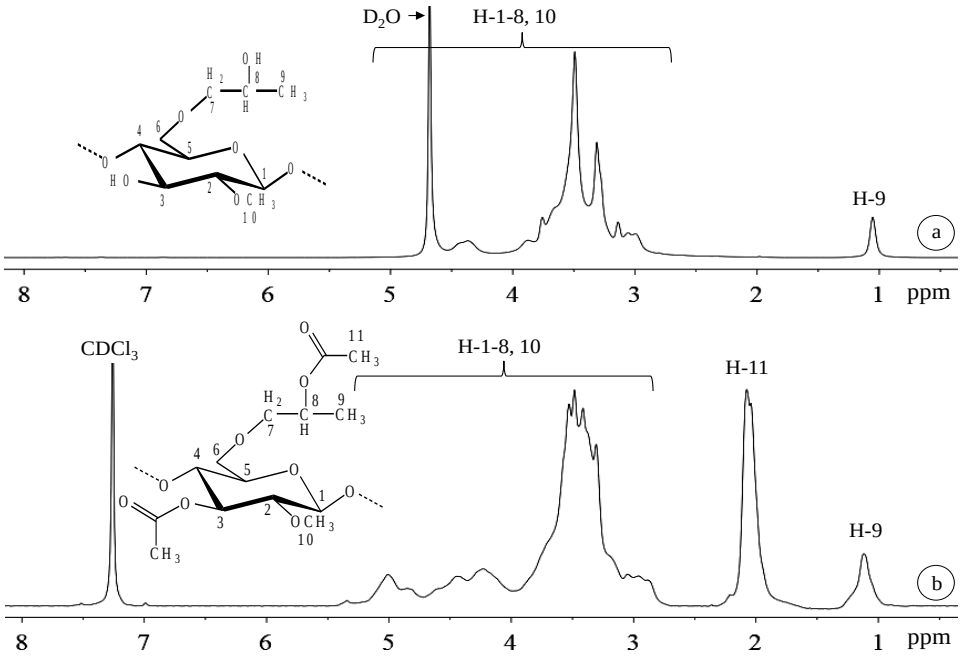

Figure 2: ^{1}H NMR (300 MHz) spectra of pure HPMC (a) and acetylated HPMC (b)

^{1}H NMR spectroscopic analysis

The success of acetylation of any polysaccharide material can be easily judged from the ^{1}H-NMR spectroscopic analysis. The incorporation of methyl of acetyl in HPMC appeared as a distinct signal at δ 2.09 (H-11) ppm and was easily recognizable. The typical ^{1}H-NMR spectrum ($CDCl_3$) of HPMC acetate **3** indicated a highly pure product and is shown in Figure 2 along with the spectrum of pure HPMC for comparison. In the spectrum of HPMC acetate, the polymer repeating unit protons showed resolved signals at δ 2.89-5.04 (H-1-8, 10) ppm, as compared to unmodified HPMC repeating unit. The methyl of hydroxypropyl moieties of HPMC appeared at δ 1.13 ppm as a broad signal. Besides the success of acetylation of HPMC, the ^{1}H-NMR spectrum of HPMC acetate has proved the purity of the product, as no signal of any impurity was noted in the spectrum.

Thermal studies

Studies on the thermal stability and thermal degradation kinetics of materials provide valuable information about their handling and storage. Thermal analysis is also important to evaluate the performance parameters of such materials for potential pharmaceutical applications.[29,30] Therefore, the thermal analysis of HPMC and HPMC acetate **3** was carried out to evaluate their thermal stability in terms of energy of activation (*Ea*), order of reaction (*n*) and different thermodynamic parameters, *etc*.

The TG and DTG curves of HPMC and HPMC acetates were recorded from room temperature to 800 °C at multiple heating rates under nitrogen atmosphere. All the TG, DTG and 2DTG curves of the HPMC and HPMC acetates acquired at accelerated rates are presented in Figures 3-5. It is clear from the thermograms that both materials exhibit a major weight loss (84 to 82%, respectively) in single step decomposition. It is also noteworthy that when increasing the heating rate (β), the values of the degradation temperatures also increase. The ranges of Tdi, Tdm and Tdf values for the major degradation step of HPMC were found to be 253-274, 337-359 and 374-391 °C, respectively. Tdi, Tdm and Tdf values for HPMC acetates were found a bit higher than those for unmodified HPMC, indicating somewhat enhanced thermal stability imparted due to acetylation (Table 2).

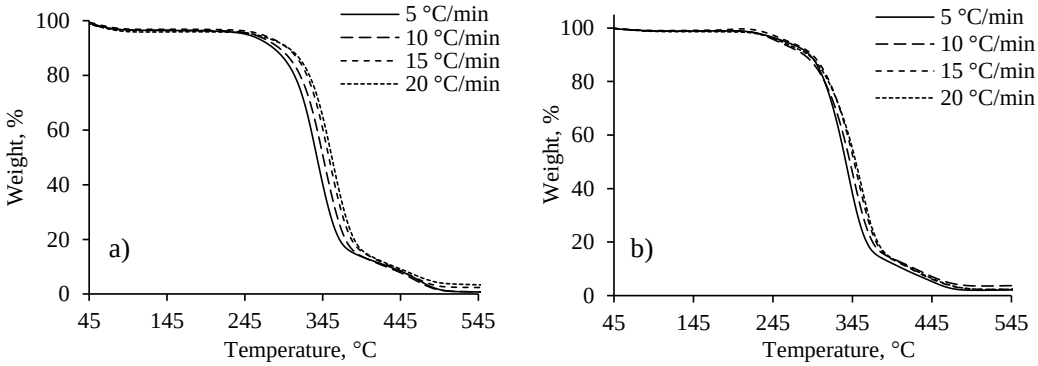

Figure 3: Overlay TG curves of HPMC (a) and HPMC acetates (b) at multiple heating rates

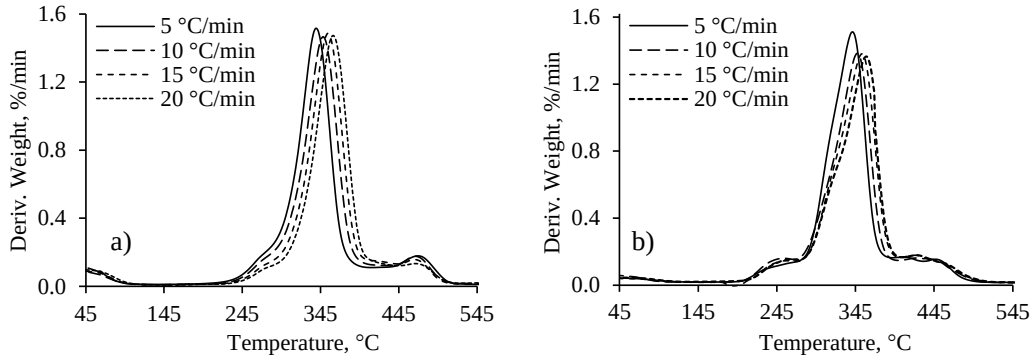

Figure 4: Overlay DTG curves of HPMC (a) and HPMC acetates (b) at multiple heating rates

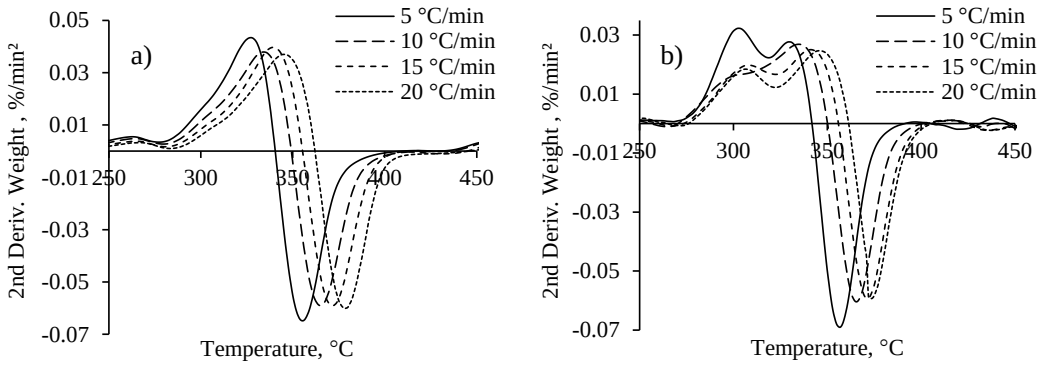

Figure 5: Overlay 2DTG curves of HPMC (a) and HPMC acetates (b) at multiple heating rates

Table 2
Thermal decomposition temperatures of HPMC and HPMC acetate at various heating rates

Sample	Step	Tdi (°C)	Tdm (°C)	Tdf (°C)	Weight loss (%) at Tdf	Char yield (wt%)
HPMC	I	253-274	337-359	374-391	82-84	2.9 at 600 °C
HPMC acetate	I	265-278	344-362	383-399	81-82	1.5 at 600 °C

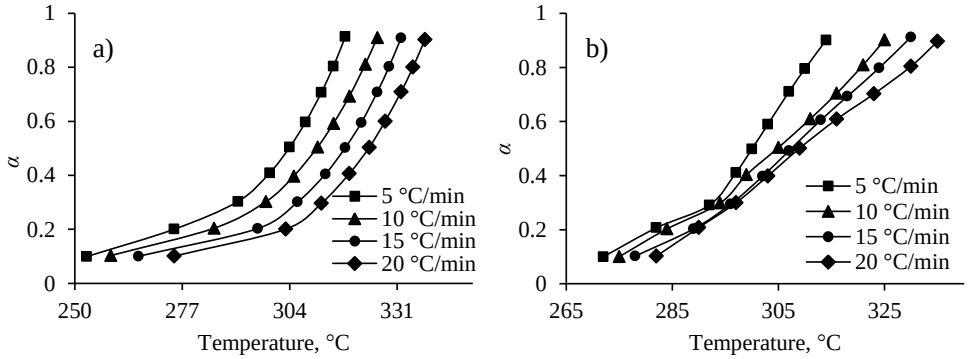

Figure 6: *α vs.* temperature curves of major thermal degradation step of HPMC (a) and HPMC acetate (b) at multiple heating rates

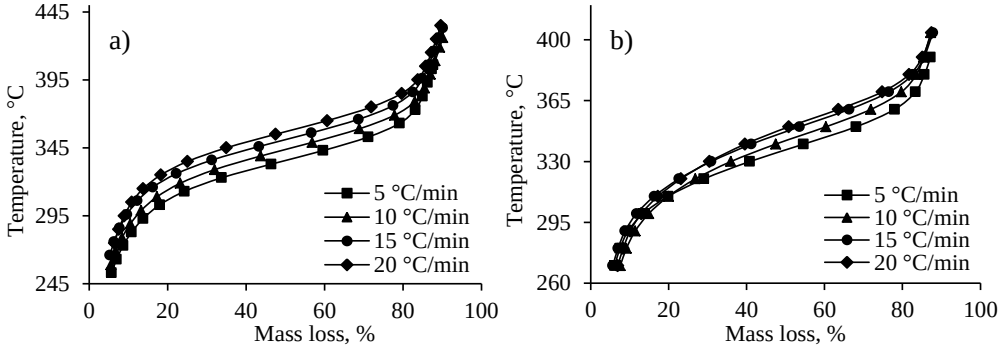

Figure 7: Mass loss % *vs.* temperature curves of major thermal degradation step of HPMC (a) and HPMC acetate (b) at multiple heating rates

Both HPMC and HPMC acetate contain carbon, hydrogen and oxygen elements only, that is why the major degradation products are gaseous in nature and minimal residue is left at the end of complete degradation.

The effects of temperature on α at multiple heating rates were compared for both materials by plotting graphs between α and T, which are shown in Figure 6. Another graph was plotted between temperature and % mass loss for each material, which is given in Figure 7.

Evaluation of degradation kinetics

The Flynn-Wall-Ozawa (FWO) isoconversional method was applied on thermal data to calculate *Ea* and frequency factor (*A*). Almost parallel straight lines were obtained when a graph was plotted between the logarithm of heating rate (log β) and 1000/*T* (Fig. 8) for various values of α. There was no variation in the *Ea* values of degradation calculated at various α values and the mean *Ea* value was found to be 104.69 kJ/mol for HPMC. Likewise, the mean *Ea* value for HPMC acetate **3** evaluated was 175.76 kJ/mol. A plot between *Ea vs.* α was also drawn for each material to observe the effect of the conversion rate on activation energy and is presented in Figure 9. Almost no significant change in the activation energy of each material at various α values can be attributed to the fact that the heating rates have no significant effect on α. Both *Ea* and *A* were found to increase significantly after acetylation of HPMC. The order (*n*) of the thermal degradation reaction of each material was found to be first order according to Kissinger's method.

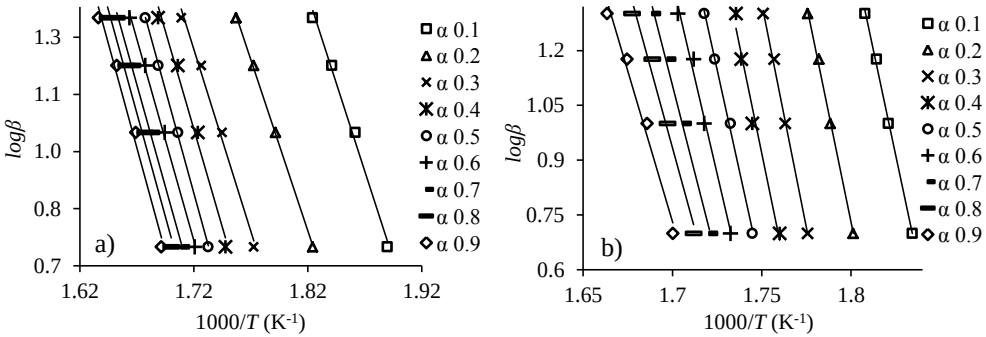

Figure 8: Flynn-Wall-Ozawa (FWO) plot between log β and 1000/T (K^{-1}) of major thermal degradation step for HPMC (a) and HPMC acetate (b) at several degree of conversion

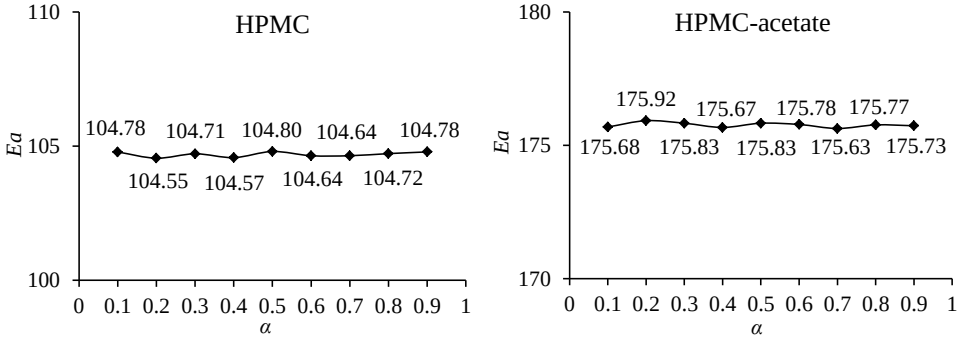

Figure 9: Plot of *Ea vs.* α indicating dependence of *Ea* on α for HPMC and HPMC acetate

Table 3
Thermal degradation kinetics and thermodynamic parameters of HPMC and HPMC acetate

Sample	Method	Step	|r|	*n*	*Ea* (kJ/mol)	ln*A*	Δ*H** (kJ/mol)	Δ*S** (J/K)	Δ*G** (kJ/mol)	IPDT	ITS
HPMC	FWO	I	0.970	-	104.69	17.50	99.81	-114.68	171.04	354	0.49
	Kissinger	I	-	1	-	-	-	-	-	-	-
HPMC acetate	FWO	I	0.975	-	175.76	29.46	170.74	-16.26	180.92	362	0.54
	Kissinger	I	-	1	-	-	-	-	-	-	-

Evaluation of thermodynamic and intrinsic thermal stability

The TG data of both HPMC and HPMC acetates were subjected to the Eyring and Polanyi method for the calculation of ΔH^*, ΔG^* and ΔS^* values (Table 3). The higher ΔH^* value for HPMC acetate **3** is another indication of thermal stability. Thermal stability is also evaluated in terms of IPDT and ITS values from the area under the TG curve. The mean IPDT and ITS values for HPMC were found to be 354 °C and 0.49, respectively, whereas, for HPMC acetate the mean IPDT value was found to be 362 °C and the ITS value was 0.54, both values being higher than those for unmodified HPMC, hence indicating greater thermal stability of the HPMC acetate than that of HPMC.

CONCLUSION

Herein, we reported a green, economical and efficient method for the acetylation of HPMC to make MCEE. HPMC acetate with a DS of 2.53 was synthesized with greater efficiency. The presented method requires less time, moderate temperature, easy work-up procedure and less energy. The catalyst used was iodine, which is a cheap, commercially available, non-degradative to glycosidic linkages and environment-friendly reagent, hence this reaction methodology can be adopted on commercial scale for the acetylation of polysaccharides and for the synthesis of different MCEE. Isoconversional thermal studies of both materials revealed that HPMC acetate is significantly more stable than HPMC. Such thermally stable and commercially important MCEE could be a useful material for potential applications in formulation design and drug recrystallization.

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