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Characterization of hydroxypropylmethylcellulose films using microwave non-destructive testing technique

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Abstract

The applicability of microwave non-destructive testing (NDT) technique in characterization of matrix property of pharmaceutical films was investigated. Hydroxypropylmethylcellulose and loratadine were selected as model matrix polymer and drug, respectively. Both blank and drug loaded hydroxypropylmethylcellulose films were prepared using the solvent-evaporation method and were conditioned at the relative humidity of 25, 50 and 75% prior to physicochemical characterization using microwave NDT technique as well as ultraviolet spectrophotometry, differential scanning calorimetry (DSC) and Fourier transform infrared spectroscopy (FT-IR) techniques. The results indicated that blank hydroxypropylmethylcellulose film exhibited a greater propensity of polymer–polymer interaction at the O–H and C–H domains of the polymer chains upon conditioned at a lower level of relative humidity. In the case of loratadine loaded films, a greater propensity of polymer–polymer and/or drug–polymer interaction via the O–H moiety was mediated in samples conditioned at the lower level of relative humidity, and via the C–H moiety when 50% relative humidity was selected as the condition for sample storage. Apparently, the absorption and transmission characteristics of both blank and drug loaded films for microwave varied with the state of polymer–polymer and/or drug–polymer interaction involving the O–H and C–H moieties. The measurement of microwave NDT test at 8 GHz was sensitive to the chemical environment involving O–H moiety while it was greatly governed by the C–H moiety in test conducted at a higher frequency band of microwave. Similar observation was obtained with respect to the profiles of microwave NDT measurements against the state of polymer–polymer and/or drug–polymer interaction of hydroxypropylmethylcellulose films containing chlorpheniramine maleate. The microwave NDT measurement is potentially suitable for use as an apparent indicator of the state of polymer–polymer and drug–polymer interaction of the matrix.

Keywords: Hydroxypropylmethylcellulose; Loratadine; Microwave; Non-destructive testing technique

1. Introduction

The transdermal drug delivery system is commonly designed to deliver the drug at a constant rate for a period of several hours to days following its application onto the skin. In the case of the latter, the transdermal drug delivery system is suitable for use in the treatment of chronic diseases whereby the patients are otherwise required to carry around the oral medications and make a conscious effort to adhere to the given dosage regimen. The basic components of a transdermal drug delivery system include drug(s) embedded in an inert polymer film, outer backing film of paper, plastic or metal foil, and a pressure sensitive adhesive which anchors these films to the skin. Examples of drugs delivered using the transdermal route are fentanyl, testosterone, clonidine and nicotine [1–4].

Quality control of matrix characteristics, such as state of polymer–polymer and drug–polymer interaction, is utmost important with respect to the therapeutic effectiveness of a transdermal drug delivery system. In the pharmaceutical industry, the analytical techniques such as Fourier-transform infrared spectroscopy and differential scanning calorimetry have long been employed to determine the matrix characteristics of the transdermal drug delivery system [5–14]. These techniques complementarily provide greater details and reinforce the findings of the matrix characteristics obtained from each other.

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Lately, the microwave has been used in replacement of chemicals to test the dielectric property of the engineering materials [15–18]. The present study sets to explore the applicability of microwave as an optional tool to characterize the matrix property of polymer film for use as a transdermal drug delivery system. A microwave-based analytical technique is built. Characterization of the polymer matrix using such technique does not require sample destruction during the process of measurement. The sample is recoverable from test and analysis of the entire batch of samples is possible without the need of solvents and chemical reagents.

2. Materials and methods

2.1. Materials

Hydroxypropylmethylcellulose (HPMC Methocel*K100 Premium LV, The Dow Chemical Company, USA) was used as a matrix polymer for the fabrication of film with loratadine (Morepen Laboratories, India) and chlorpheniramine maleate (Sigma, Germany) as the model drugs. Hydrochloric acid (analytical grade, Merck, Germany) was employed in drug content assay. Lithium chloride (Acros Organics, USA), chromium(VI) oxide (Acros Organics, USA) and sodium chloride (Merck, Germany) were used as chemicals for the control of the relative humidity of storage chamber.

2.2. Methods

2.2.1. Preparation of film

An accurately weighed 1.5 g of 2.5% (w/w) HPMC solution, with or without loratadine, was transferred into a glass Petri dish (internal diameter = 3 cm). The solution was then subjected to hot air drying at $40 \pm 0.5\,^{\circ}C$ for 24 h. The formed film was collected and further conditioned in a desiccator at $25 \pm 1\,^{\circ}C$ and at a pre-set level of relative humidity for at least 5 days prior to physicochemical characterization. The theoretical content of HPMC in each blank (A0) and drug loaded polymer films (A1, A2, A3 and A4) was kept at 37.5 mg. In the case of drug loaded HPMC films, 5, 10, 20 and 40 mg of loratadine were added into the formed films denoted as A1, A2, A3 and A4, respectively. At least triplicates were carried out for each formulation. The pre-set levels of relative humidity were kept at 25 ± 5, 50 ± 5 and $75 \pm 5\%$ using the saturated solutions of lithium chloride, chromium(VI) oxide and sodium chloride, respectively.

2.2.2. Characterization of films

The drug content and thickness of film were examined using ultraviolet spectrophotometry and digital caliper system, respectively, while the matrix characteristics of film were assessed using differential scanning calorimetry (DSC), Fourier-transform infrared spectroscopy (FT-IR) and microwave non-destructive testing (NDT) techniques.

2.2.2.1. Drug content analysis. An accurately weighed fraction of a film was dissolved in 0.1 M HCl solution. The content of loratadine embedded in the sample was determined spectrophotometrically at 275.1 nm (Cary 50 Conc, Varian Australia Pty Ltd., Australia). A total of five fractions from each film were assayed for the drug content. The drug content was defined as the percentage loratadine embedded in a unit weight of film. Triplicates were carried out and the results averaged. The difference in drug content between films stored at various levels of relative humidity was examined using ANOVA.

2.2.2.2. DSC analysis. DSC thermograms were obtained using a differential scanning calorimeter (Pyris 6 DSC, Perkin Elmer, USA). Three milligrams of sample were crimped in a standard aluminium pan and heated from 30 to 300 °C at a heating rate of 10 °C/min under constant purging of nitrogen at 40 ml/min. The characteristic peaks and specific heat of the melting endotherm were recorded. At least triplicates were carried out for each batch of sample and the results averaged.

2.2.2.3. FT-IR analysis. 2.5% (w/w) of sample, with respect to the potassium bromide (KBr) disc, was mixed with dry KBr (FT-IR grade, Aldrich, Germany). The mixture was ground into a fine powder using an agate mortar before compressing into a disc. Each disc was scanned at a resolution of $4\,cm^{-1}$ over a wavenumber region of 450–4000 cm^{-1} using a FT-IR spectrometer (Spectrum RX1 FTIR system, Perkin Elmer, USA). The characteristic peaks of IR transmission spectra were recorded. At least triplicates were carried out for each batch of sample and the results averaged.

2.2.2.4. Microwave NDT analysis. The self-assembled microwave NDT equipment was made of a rectangular dielectric waveguide (RDWG) system, standard-gain horn antennas, coaxial cables and a WILTRON 37269B vector network analyzer (VNA, WILTRON, USA) (Fig. 1). The RDWG was constructed using polytetrafluoroethylene (PTFE). Each RDWG had a length of 37.5 cm and was equipped with a standard metallic TE_{10} waveguide (WR-90) of which acted as a microwave launcher for the RDWG. The RDWG was inserted

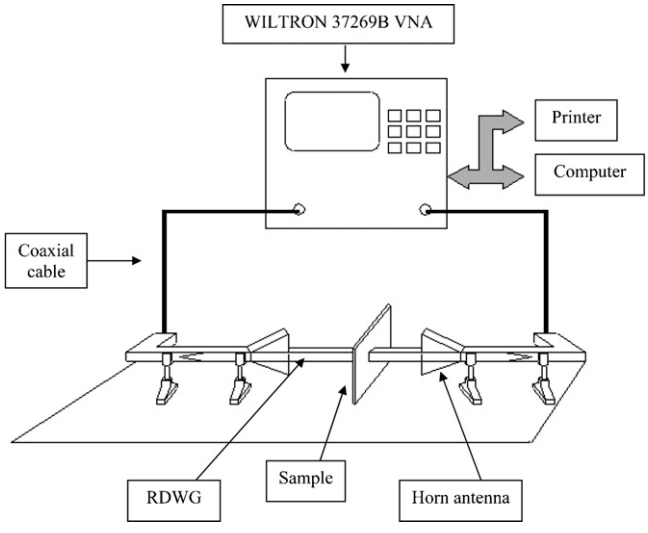

Fig. 1. Rectangular dielectric waveguide (RDWG) measurement system.

into the WR-90 waveguide through a standard-gain horn antenna of which functioned to contain and minimize the losses of microwave from RDWG. At the point of insertion into each WR-90 waveguide, the edge of RDWG was double-tapered to direct the transmission of microwave across the RDWG. The contact area of RDWG with film had a cross-sectional area of 22.86 mm × 10.16 mm. It had a smooth surface in order to avoid the formation of air pockets between the surfaces of RDWG and film.

The measurement system of RDWG was calibrated using the internal Through, Reflect and Line model of VNA. The amplitudes of forward transmission coefficient (S_{21}) and forward reflection coefficient (S_{11}) were characterized. The accuracy of RDWG system was verified through the measurement of complex permittivities of samples with known dielectric properties such as PTFE and plexiglass prior to its application in film characterization [19–22].

The characterization of film using the microwave NDT technique proceeded by first placing the test sample directly in contact with two RDWGs on the opposite sides of the film. S_{11} and S_{21} values of the film were determined at various spots of the same sample using the microwave frequency at 8 and 12 GHz. The power transmission coefficient (nPTC), power reflection coefficient (nPRC) and power absorption coefficient (nPAC) of samples were calculated using the following equations:

$$\text{nPTC}\,(\%) = \frac{|S_{21}|^2_{\text{linear}} \times 100}{d} \quad (1)$$

$$\text{nPRC}\,(\%) = \frac{|S_{11}|^2_{\text{linear}} \times 100}{d} \quad (2)$$

$$\text{nPAC}\,(\%) = \frac{\left[1 - |S_{11}|^2_{\text{linear}} - |S_{21}|^2_{\text{linear}}\right] \times 100}{d} \quad (3)$$

where $|S_{11}|_{\text{linear}} = 10^{(|S_{11}|_{\text{dB}}/20)}$, $|S_{21}|_{\text{linear}} = 10^{(|S_{21}|_{\text{dB}}/20)}$ and d is the film thickness of which was measured using a digital micrometer (Mitutoyo, Japan). Triplicates were carried out for each batch of sample and the results averaged. Principally, microwave possesses both electrical and magnetic properties. The contact of microwave with an object results in vibration of molecules by induced or permanent dipoles. The intensity of vibration is a function of the quantity of microwave energy absorbed by the object [23]. This depends on the size, shape and polarizability of the molecules, as well as, extent of intermolecular interaction of the object. Apparently, materials with a high level of molecular interaction are expected to absorb more microwave energy, thereby giving rise to a more intense vibration.

2.2.3. Challenge test

HPMC films containing 5 mg (B1) and 20 mg (B2) of chlorpheniramine maleate were prepared, stored and characterized in the similar manner as those of loratadine loaded samples except that the deionized water was used as a solvent in drug content analysis of films. The profiles of microwave NDT measurement of chlorpheniramine maleate loaded films were examined with respect to the state of polymer-polymer and/or drug–polymer interaction of the matrices and were compared to those obtained from films prepared using the loratadine as a model drug.

3. Results and discussion

Table 1 shows the contents of loratadine embedded in HPMC films determined using the ultraviolet spectrophotometry. The drug content of films was not affected by the level of relative humidity in the storage chamber (ANOVA: $p > 0.05$). Practically, a flat film was formed with the incorporation of drug load up to approximately 60% (w/w), expressed with respect to the weight of the film. The thickness of HPMC films varied with the amount of drug load employed (Table 1). Generally, a thicker film was formed in sample containing a higher content of drug load.

In the present investigation of the applicability of microwave NDT technique to characterize the matrix property of the polymer film, the nPTC, nPRC and nPAC values of each film were computed. The magnitude of nPTC, nPRC and nPAC represented the propensity of microwave being transmitted through, reflected from and absorbed into the film. Their applicability in film characterization was assessed in relation to thermograms and spectra of film obtained from DSC and FT-IR analysis, respectively.

3.1. DSC analysis

DSC analysis showed that the unprocessed HPMC had two melting endotherms (Table 2a; Fig. 2a). The melting peak temperatures of these endotherms decreased whereas the enthalpy values of these endotherms increased upon conversion of the unprocessed HPMC into film A0 stored under the relative humidity of 25, 50 and 75% (Tables 2a and 3). The film stored under a lower level of relative humidity had higher melting peak temperatures, but lower endothermic enthalpy value at specific domains of the HPMC in film (Table 3). The results indicated that there was a reduction in the strength of polymer–polymer interaction in film when the sample was conditioned at a higher level of relative humidity. On the other hand, the extent of polymer–polymer interaction of the same sample might be enhanced and/or this sample contained a higher level of sorbed moisture owing to its storage at a higher level of relative humidity. The latter observation can be aptly explained by an increase in the moisturization value of films from 3.57 ± 0.14 in samples stored under the relative humidity of 25% to 4.76 ± 0.76 in samples stored at the relative humidity of 75%, as inferred from the

Table 1
Empirical film thickness and loratadine content of HPMC films

Sample	Film thickness (mm)	Loratadine content (%, w/w)		
		25	50	75
A0	0.031 ± 0.006	0	0	0
A1	0.066 ± 0.005	13.04 ± 0.32	13.18 ± 0.28	12.97 ± 0.22
A2	0.055 ± 0.008	23.58 ± 1.28	24.57 ± 0.36	22.22 ± 0.78
A3	0.134 ± 0.022	40.90 ± 2.54	34.90 ± 0.63	37.71 ± 4.45
A4	0.128 ± 0.019	59.35 ± 2.78	58.14 ± 4.25	57.26 ± 3.94

The values 25, 50, and 75 denote relative humidity (%).

Table 2
DSC and FT-IR profiles of unprocessed HPMC, loratadine and chlorpheniramine maleate

Sample	T_g[a] (°C)	T_m[b] (°C)	ΔH[c] (J/g)
(a) DSC			
HPMC	84.9 ± 2.5	153.5 ± 1.0	7.3 ± 0.4
		180.5 ± 2.0	54.1 ± 7.8
Loratadine	–	138.3 ± 0.2	81.4 ± 1.2
Chlorpheniramine maleate	–	135.4 ± 0.2	121.3 ± 5.1

Sample	Wavenumber (cm^{-1})	Functional group
(b) FT-IR		
HPMC	1459.3 ± 1.4	C–H
	1650.6 ± 1.2	C=O of glucose unit
	2937.3 ± 0.6	C–H
	3465.3 ± 3.9	O–H
	900–1300	C–O–C
Loratadine	1222.4 ± 0.8	C–O, C–N
	1696.9 ± 2.1	C=O, C–N and/or unconjugated C=C
	2900.2 ± 3.7	C–H
	2982.6 ± 0.1	C–H
Chlorpheniramine maleate	1489.7 ± 0.6	C=O, C–N and/or aromatic C=C
	1489.7 ± 0.6	C–H
	2968.2 ± 0.3	C–H
	3376.5 ± 8.2	N–H
	3487.2 ± 2.8	N–H

[a] Glass transition temperature.
[b] Melting peak temperature.
[c] Enthalpy.

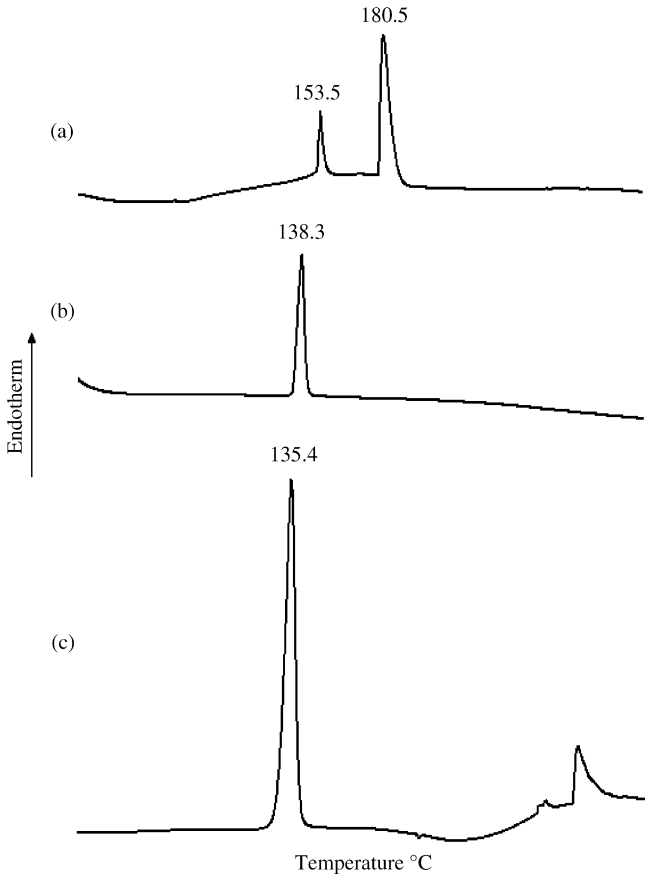

Fig. 2. DSC thermograms of (a) unprocessed HPMC, (b) loratadine and (c) chlorpheniramine maleate.

changes in capacitance values obtained using the skin hydration measurement device (Corneometer® CM825, Cologne, Germany) of which a higher moisturization value represented the presence of a higher content of sorbed moisture in the test samples. Incidentally, the film stored under a higher level of relative humidity had a lower glass transition temperature (Table 3). The sorbed moisture interacted with the film via a plasticization action thereby leading to a reduction in the glass transition temperature of sample stored at a higher level of relative humidity.

Incorporation of loratadine into the HPMC film brought about the formation of new endotherms at about 114–122 °C of samples stored under the relative humidity of 25, 50 and 75% (Table 3). Apparently, the loading of loratadine into the HPMC film brought about a reduction in the melting peak temperature of the unprocessed drug at 138.3 ± 0.2 °C, probably due to the interruption of drug crystals by the presence of HPMC (Tables 2a and 3; Fig. 2b). The melting peak temperature of loratadine was lower in film stored at a higher level of relative humidity (Table 3). An increase in drug content of films from samples A1 to A4 was reflected by an increase in the enthalpy value of these endotherms (Table 3).

In addition to the newly formed endotherm, two melting endotherms attributed to the different domains of HPMC molecules were found in the thermogram of the drug-loaded film (Tables 2a and 3). Similar to those of blank HPMC films A0, the melting peak temperatures were comparatively higher in film stored at a lower level of relative humidity particularly when samples A2, A3 and A4 were concerned. Keeping the drug content similar, higher endothermic enthalpy values were obtained at various HPMC domains when the sample was kept at a higher level of relative humidity unlike the case of blank HPMC film A0 of which the changes of enthalpy were restricted to the specific domain of HPMC molecules in film (Table 3). This was aptly explained by the interaction between the drug and polymer at various domains of the latter in drug-loaded film. At a higher level of relative humidity, the glass transition temperatures of the drug loaded HPMC films were lower (Table 3). Similar to blank HPMC film A0, the sorbed moisture had have interacted with the film and resulted in a reduction in the glass transition temperature of sample stored at a higher level of relative humidity.

3.2. FT-IR analysis

Fig. 3a as well as Tables 2b and 4 show the FT-IR profiles of the unprocessed HPMC, and the characteristic FT-IR peaks of samples A0 stored at the relative humidity of 25, 50 and 75%. The HPMC molecules in films stored at the relative humidity of 25 and 50% exhibited a greater strength of interaction via the polymeric O–H and C–H functional groups than that of unprocessed HPMC and film stored at the relative humidity of 75%. Apparently, the conversion of unprocessed HPMC into film did

Table 3
DSC glass transition temperatures, melting peak temperatures and enthalpy values of HPMC films

Sample	Relative humidity (%)								
	25			50			75		
	T_g[a] (°C)	T_m[b] (°C)	ΔH[c] (J/g)	T_g (°C)	T_m (°C)	ΔH (J/g)	T_g (°C)	T_m (°C)	ΔH (J/g)
A0	71.4 ± 1.5	148.6 ± 1.8	23.3 ± 3.1	69.8 ± 2.2	145.0 ± 2.0	22.3 ± 2.2	54.6 ± 10.3	140.7 ± 0.9	21.5 ± 3.2
		178.7 ± 4.6	60.5 ± 6.4		156.4 ± 2.4	106.1 ± 11.9		154.0 ± 4.4	151.1 ± 12.2
A1	83.1 ± 5.4	117.4 ± 0.7	6.7 ± 0.6	80.4 ± 2.4	117.0 ± 0.3	8.0 ± 1.2	54.8 ± 4.4	114.4 ± 0.3	7.1 ± 0.7
		145.6 ± 0.4	20.7 ± 0.2		144.7 ± 1.3	22.9 ± 1.4		141.0 ± 2.5	23.8 ± 0.5
		175.7 ± 2.7	59.4 ± 4.9		172.1 ± 1.4	68.5 ± 6.1		166.2 ± 5.1	99.1 ± 14.0
A2	85.9 ± 4.6	117.7 ± 0.4	12.2 ± 1.1	76.6 ± 8.9	117.2 ± 0.3	14.5 ± 0.8	60.3 ± 4.5	114.4 ± 0.2	15.3 ± 1.6
		148.3 ± 3.0	19.1 ± 1.2		147.9 ± 3.3	19.9 ± 2.2		142.0 ± 1.7	25.1 ± 0.8
		180.9 ± 3.2	45.5 ± 6.8		182.9 ± 3.4	45.6 ± 5.6		161.2 ± 1.3	105.6 ± 18.1
A3	86.5 ± 7.8	121.7 ± 1.6	28.3 ± 3.4	69.8 ± 7.3	117.2 ± 0.3	27.6 ± 1.1	57.1 ± 0.0	114.7 ± 0.3	23.9 ± 2.9
		159.9 ± 3.8	8.8 ± 1.6		148.3 ± 0.9	18.3 ± 1.8		145.8 ± 0.5	22.8 ± 1.3
		224.6 ± 10.4	16.4 ± 1.0		184.5 ± 4.0	37.2 ± 5.5		176.1 ± 3.3	53.2 ± 4.2
A4	80.7 ± 8.9	119.9 ± 0.9	43.3 ± 1.0	82.3 ± 10.1	118.2 ± 0.5	39.6 ± 3.0	66.1 ± 4.8	115.9 ± 0.3	42.1 ± 1.6
		160.5 ± 1.3	6.8 ± 0.8		152.9 ± 1.7	11.5 ± 1.1		150.7 ± 1.4	14.8 ± 2.0
		220.5 ± 1.3	14.4 ± 0.3		202.2 ± 6.4	20.7 ± 0.4		194.0 ± 1.6	27.8 ± 3.1
B1	100.2 ± 4.0	159.3 ± 3.2	13.0 ± 1.4	81.1 ± 3.5	151.1 ± 2.2	19.5 ± 2.6	99.9 ± 3.6	142.4 ± 0.8	25.2 ± 2.3
		206.6 ± 2.6	33.4 ± 1.4		187.2 ± 1.0	50.9 ± 2.7		165.3 ± 2.3	117.3 ± 10.1
B2	92.8 ± 7.9	162.3 ± 1.7	12.1 ± 1.7	90.2 ± 3.9	156.8 ± 2.0	16.1 ± 1.5	99.4 ± 7.9	147.4 ± 1.2	22.4 ± 1.6
		196.6 ± 2.4	39.5 ± 3.0		187.2 ± 0.9	45.6 ± 5.1		182.5 ± 3.5	82.5 ± 11.7

[a] Glass transition temperature.
[b] Melting peak temperature.
[c] Enthalpy.

Table 4
FT-IR peak wavenumber values of HPMC films

Sample	Wavenumber (cm^{-1})			Functional group
	25	50	75	
A0	1450.4 ± 1.4	1449.6 ± 1.5	1452.4 ± 1.0	C–H
	2924.5 ± 5.2	2917.7 ± 8.4	2926.1 ± 9.7	C–H
	3372.5 ± 69.7	3296.9 ± 50.7	3461.0 ± 8.8	O–H
A1	2925.8 ± 2.4	2911.8 ± 5.9	2926.1 ± 2.0	C–H
	3438.6 ± 5.9	3425.7 ± 4.2	3419.5 ± 10.2	O–H
	Increasing dual crest demarcation with relative humidity of peaks at: 1647.1 ± 5.1 cm^{-1}; 1700.0 ± 2.6 cm^{-1}			C=O; C=O, C–N and/or C=C
A2	2925.9 ± 0.4	2905.5 ± 2.8	2921.4 ± 8.4	C–H
	3410.9 ± 11.5	3425.7 ± 11.4	3435.4 ± 6.9	O–H
A3	1227.7 ± 0.4	1226.4 ± 0.0	1223.3 ± 0.7	C–O, C–N
	2925.0 ± 0.6	2906.7 ± 1.0	2912.2 ± 9.8	C–H
	3408.6 ± 4.1	3419.7 ± 8.8	Band broadening	O–H
A4	1382.7 ± 0.0	1383.2 ± 1.1	Peak loss	C–O, C–N
	2925.4 ± 0.4	2871.9 ± 8.6	2902.6 ± 1.3	C–H
	3424.9 ± 9.2	3431.1 ± 7.9	Band broadening	O–H
	Gradual disappearance of dual crest demarcation of peaks at 1600–1700 cm^{-1}			C=O, C–N and/or C=C
B1	2941.7 ± 3.8	2926.3 ± 4.4	2924.9 ± 4.2	C–H
	3490.1 ± 9.2	3442.1 ± 10.9	3390.1 ± 9.0	O–H, N–H
			3490.4 ± 7.6	
B2	1466.9 ± 1.4	1478.8 ± 2.5	Gradual peak loss	C–H
	3436.7 ± 4.2	3476.1 ± 3.3	3361.5 ± 5.1	O–H, N–H
			3502.2 ± 1.3	

The values 25, 50, and 75 denote relative humidity (%).

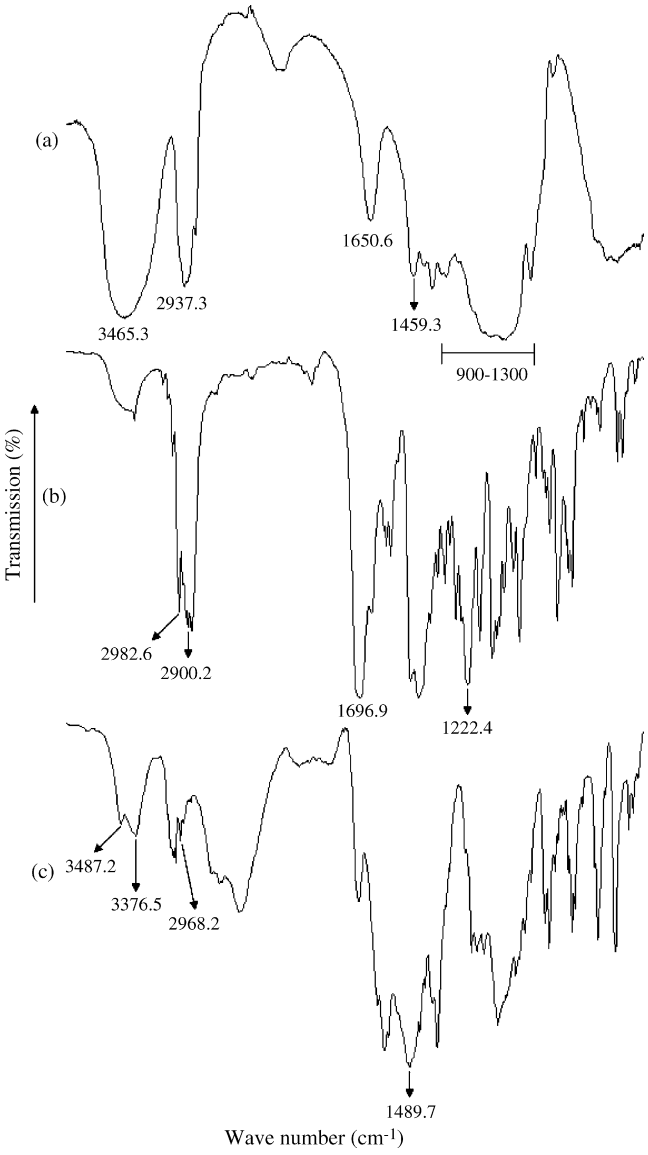

Fig. 3. FT-IR spectra of (a) unprocessed HPMC, (b) loratadine and (c) chlorpheniramine maleate.

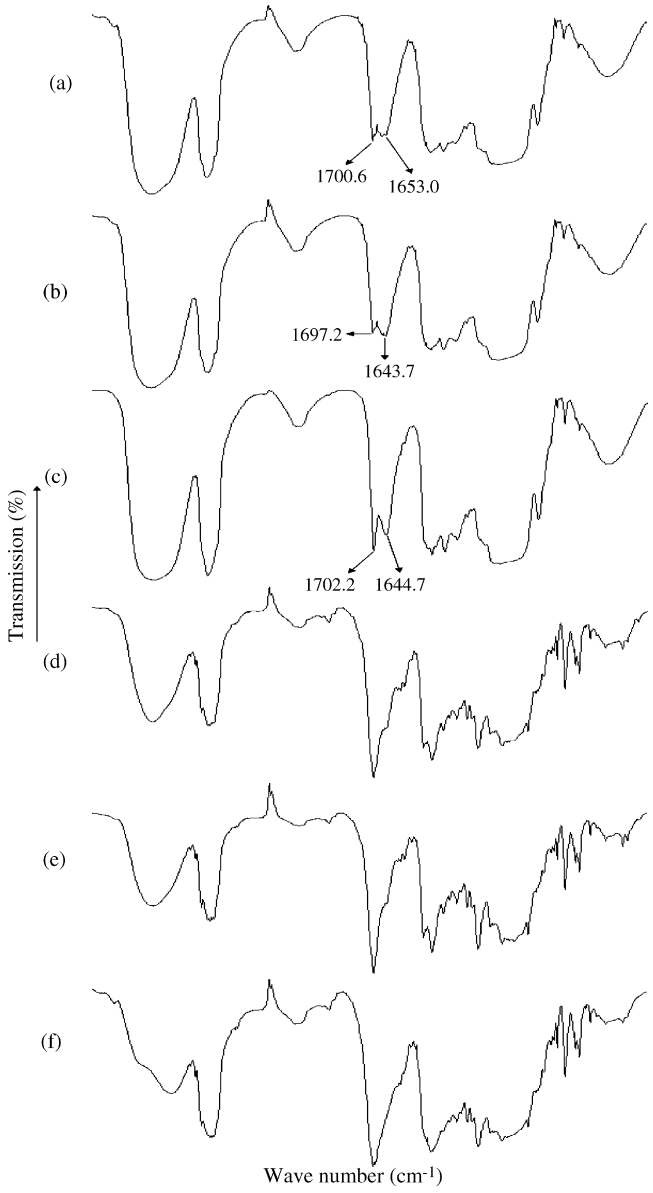

Fig. 4. FT-IR spectra of (a) A1: 25% RH, (b) A1: 50% RH, (c) A1: 75% RH, (d) A4: 25% RH, (e) A4: 50% RH and (f) A4: 75% RH.

not result in a net dissociation of polymer chains via specific functional groups. The reduction in the DSC melting peak temperatures of the film samples was possibly ascribed to a decrease in the physical entanglement of the HPMC molecules upon their conversion into film. In the case of samples A0 stored at a lower level of relative humidity, the DSC melting peak temperatures were higher than that of stored at a higher level of relative humidity as further interactions between the HPMC molecules via O–H and C–H moieties were effected in the former.

Incorporation of loratadine into the HPMC film brought about varying changes to the FT-IR spectra of samples A0. Analysis of the FT-IR spectra indicated that there was a lower propensity of drug–polymer interaction in film A1 stored at the relative humidity of 75% via the C=O of polymer and C=O, C–N and/or unconjugated C=C of drug as the FT-IR peak at the wavenumber region between 1600 and 1700 cm^{-1} exhibited a clear demarcation of dual crest (Table 4; Fig. 4a–c). The present observation was further supported by the difference in the DSC melting peak temperatures of drug in sample A1 stored at varying levels of relative humidity (Table 3). The sample A1 also showed a greater strength of polymer–polymer and/or drug–polymer interaction via the C–H functional group as indicated by a lower FT-IR wavenumber obtained at $2911.8 \pm 5.9\,cm^{-1}$ when it was kept at the relative humidity of 50% (Table 4).

With the incorporation of higher drug loads in the HPMC films, namely A2, A3 and A4, the propensity of polymer–polymer and/or drug–polymer interaction via the O–H moiety became greater in samples stored at a lower level of relative humidity. The FT-IR wavenumbers of sample A2 stored at a lower level of relative humidity were smaller than that of kept at a higher level of relative humidity (Table 4). The FT-IR wavenumbers of samples A3 and A4 stored at the relative humidity of 25 and 50% were 3408.6 ± 4.1 and $3424.9 \pm 9.2\,cm^{-1}$,

and 3419.7 ± 8.8 and 3431.1 ± 7.9 cm^{-1}, respectively, whereas a band broadening was noted at the similar FT-IR wavenumber region in the case of samples A3 and A4 stored at the relative humidity of 75% (Table 4). Apparently, the FT-IR wavenumber ascribing C–N and/or C–O moiety tend to become smaller with sample A3 stored at a higher level of relative humidity (Table 4). The sample A4 stored at the relative humidity of 25 and 50% had an average FT-IR wavenumber of 1383 ± 0.3 cm^{-1}. Upon storage of the same sample at the relative humidity of 75%, a lost of the resultant FT-IR peak was found indicating that the drug–polymer interaction might be mediated via the C–O and/or C–N functional groups of HPMC and loratadine. The drug–polymer interaction could also have effected via the C=O of polymer and C=O, C–N and/or unconjugated C=C of drug in sample A4 stored at the relative humidity of 75%. In the latter, an excessively high level of relative humidity could have promoted the drug–polymer interaction to varying extents as marked by a gradual disappearance of the dual crest characteristics of FT-IR peak at the wavenumber region between 1600 and 1700 cm^{-1} (Table 4; Fig. 4d–f).

Under the storage condition with a relative humidity of 50%, incorporating high drug loads in the HPMC films promoted the polymer–polymer and/or drug–polymer interaction via the C–H functional groups particularly when samples A2, A3 and A4 were concerned. The FT-IR wavenumbers of these samples were relatively smaller than those of kept at the lower or higher levels of relative humidity (Table 4).

The DSC thermal profiles of the drug-loaded films were dependent on the net effects of polymer–polymer and/or drug–polymer interaction in the formed matrix. Practically, the polymer–polymer and/or drug–polymer interaction could be effected via chemical bonding between the functional moieties such as O–H, C–H, C–N, C–O, C=O and/or C=C in addition to physical association between the polymer chains and/or drug molecules. With respect to films made of HPMC, the strength of polymer–polymer and/or drug–polymer interaction appeared to be higher in samples stored at a lower level of relative humidity, independent of the drug load contained in the matrices.

3.3. Microwave NDT analysis

The microwave NDT analysis indicated that the nPAC, nPTC and nPRC values of both blank and drug loaded films obtained at the frequency bands of 8 and 12 GHz varied with the profiles of polymer–polymer and drug–polymer interaction in films. As the values of nPRC were relatively small and susceptible to erroneous variation, the subsequent discussion would thus focus on the measurements of nPTC and nPAC as the indicator of matrix characteristics in addition to thermal and molecular spectroscopy profiles obtained using the DSC and FT-IR techniques, respectively.

Using a microwave frequency of 8 GHz, it was found that a higher nPAC, but a lower nPTC values were obtained with both blank and drug loaded films stored at a lower level of relative humidity (Table 5a). Similar observation was found with blank HPMC films in the case of microwave NDT test conducted at the frequency of 12 GHz (Table 5b). Nevertheless, the drug loaded films stored at the relative humidity of 50% demonstrated a higher nPAC, but a lower nPTC values than those of stored at a lower or higher level of relative humidity when the microwave NDT measurement was conducted using a test frequency of 12 GHz (Table 5b). Broadly, it was noted that the blank HPMC film A0 exhibited a greater propensity of polymer–polymer interaction at the O–H and C–H domains upon storage at a lower level of relative humidity. In the case of the drug loaded films (A1, A2, A3 and A4), a greater propensity of polymer–polymer and/or drug–polymer interaction via the O–H moiety was particularly noted in samples stored at the lower level of relative humidity, and via the C–H functional group when 50% relative humidity was selected as the condition for sample storage. The results suggested that the measurement of microwave NDT test at 8 GHz was sensitive to the chemical environment of film involving the polar moiety such as O–H functional group, while it was greatly governed by the less polar moiety such as C–H functional group in tests conducted at a higher frequency band of microwave. Indeed, the sample A1 stored at the relative humidity of 50% had exhibited

Table 5
nPTC, nPRC and nPAC values of HPMC films determined at microwave frequency bands of (a) 8 GHz and (b) 12 GHz

Sample	Relative humidity (%)								
	25			50			75		
	nPTC (%/mm)	nPRC (%/mm)	nPAC (%/mm)	nPTC (%/mm)	nPRC (%/mm)	nPAC (%/mm)	nPTC (%/mm)	nPRC (%/mm)	nPAC (%/mm)
(a) 8 GHz									
A0	3088.50 ± 5.84	0.07 ± 0.01	114.28 ± 5.84	3127.79 ± 8.50	0.09 ± 0.02	74.96 ± 8.51	3172.94 ± 13.74	0.13 ± 0.02	29.78 ± 13.75
A1	1498.20 ± 3.45	0.05 ± 0.01	14.35 ± 3.45	1498.09 ± 5.23	0.05 ± 0.01	14.47 ± 5.24	1498.83 ± 7.49	0.07 ± 0.01	13.71 ± 7.49
A2	1781.55 ± 6.61	0.06 ± 0.01	32.91 ± 6.61	1781.36 ± 4.46	0.05 ± 0.01	33.11 ± 4.46	1798.56 ± 12.32	0.09 ± 0.01	15.87 ± 12.33
A3	734.28 ± 2.74	0.03 ± 0.01	9.50 ± 2.74	731.42 ± 1.95	0.03 ± 0.00	12.35 ± 1.95	738.69 ± 6.23	0.03 ± 0.01	5.08 ± 6.23
A4	762.44 ± 2.37	0.04 ± 0.00	16.74 ± 2.37	761.68 ± 5.19	0.04 ± 0.01	17.50 ± 5.19	772.43 ± 5.43	0.02 ± 0.01	6.77 ± 5.42
(b) 12 GHz									
A0	3074.47 ± 4.49	0.11 ± 0.04	128.27 ± 4.48	3114.06 ± 8.41	0.27 ± 0.05	88.52 ± 8.44	3155.45 ± 12.79	0.39 ± 0.13	47.00 ± 12.90
A1	1490.33 ± 3.42	0.18 ± 0.04	22.10 ± 3.43	1476.86 ± 4.51	0.15 ± 0.03	35.60 ± 4.53	1488.97 ± 6.96	0.24 ± 0.06	23.40 ± 6.97
A2	1771.73 ± 6.05	0.18 ± 0.06	42.61 ± 6.06	1756.83 ± 4.45	0.15 ± 0.03	57.54 ± 4.45	1788.59 ± 10.64	0.32 ± 0.08	25.60 ± 10.69
A3	737.23 ± 2.81	0.11 ± 0.03	6.46 ± 2.83	721.30 ± 1.71	0.10 ± 0.02	22.40 ± 1.73	734.10 ± 5.70	0.13 ± 0.07	9.57 ± 5.71
A4	766.18 ± 1.62	0.10 ± 0.02	12.94 ± 1.64	758.10 ± 5.07	0.14 ± 0.05	20.98 ± 5.13	766.21 ± 4.89	0.05 ± 0.05	12.97 ± 4.84

a higher nPAC but a lower nPTC values when it was subjected to microwave NDT test at 12 GHz. The same sample showed no marked difference between films kept at 25, 50 and 75% relative humidity with respect to nPAC and nPTC measurements conducted at 8 GHz. This can be aptly explained by the fact that the variation in polymer–polymer and/or drug–polymer interaction were effected largely via the C–H, but not the O–H functional groups of the matrix as indicated by the FT-IR study. Unlike the drug loaded films, the microwave NDT test of blank HPMC films A0 stored at the relative humidity of 25% as well as 50% give rise to higher nPAC, but lower nPTC values regardless of the test frequencies employed when compared to the sample stored at the relative humidity of 75%. This was attributed to a greater strength of polymer–polymer interaction was mediated in the former at both domains of O–H and C–H of film. Unexpectedly, the film sample A4 stored at the relative humidity of 75% did not exhibit a higher nPAC nor a lower nPTC value in the microwave NDT test conducted at 8 GHz than those kept at the lower relative humidity levels in spite of the FT-IR spectrum indicated a marked change in the chemical environment of matrix involving the O–H functional group. It was presumed that the interaction of O–H moiety of HPMC with hydrophobic drug could have promoted the absorption power of matrix for microwave, but to a lesser extent. The net effects of drug–polymer interaction via the O–H functional group on the magnitudes of nPAC and nPTC were comparatively minimal when compared to that of the polymer–polymer counterpart.

Unlike the FT-IR study, the trend of changes in DSC thermograms with respect to the measurements of microwave NDT analysis was less clear. The DSC endotherm was indicative of both chemical interaction as well as physical entanglement of film materials. Nonetheless, the microwave NDT analysis could be less sensitive to the physical environment of film thereby being less reflective by the outcome of DSC. In general, the Pearson correlation study indicated that both nPTC and nPAC values of drug loaded HPMC films were correlatable to the changes in O–H and C–H domains of the matrices under the influence of relative humidity (8 GHz: nPTC, $r \geq 0.79$; nPAC, $r \geq -0.79$; 12 GHz: nPTC, $r \geq 0.72$; nPAC, $r \geq -0.72$) and the degree of correlation was larger than those of the blank counterparts (8 GHz: nPTC, $r \geq 0.57$; nPAC, $r \geq -0.57$; 12 GHz: nPTC, $r \geq 0.70$; nPAC, $r \geq -0.70$).

3.4. Challenge test

Similar to loratadine loaded films, the drug content of films containing the chlorpheniramine maleate was not affected by the level of relative humidity in the storage chamber (ANOVA: $p > 0.05$). The average drug contents of films B1 and B2 were 11.24 ± 0.45 and 33.22 ± 0.78% (w/w), respectively, and a thicker film was formed in sample containing a higher content of drug load (B1: 0.043 ± 0.013 mm, B2: 0.058 ± 0.015 mm). DSC analysis indicated that the film stored under a lower level of relative humidity had higher melting peak temperatures, but lower endothermic enthalpy values at various domains of the film (Table 3). Nonetheless, there was no apparent trend with respect to the glass transition temperature.

The FT-IR analysis showed that films B1 exhibited a greater propensity of polymer–polymer and/or drug–polymer interaction via the O–H/N–H and C–H moieties when samples were stored at a higher level of relative humidity. The wavenumbers of films B1 ascribing to O–H/N–H and C–H functional groups of polymer and drug were larger in samples stored at a lower level of relative humidity than those of kept at a higher level of relative humidity (Table 4; Fig. 5a–c). In the latter, the FT-IR peak attributed to O–H and N–H moieties of polymer and drug displayed a dual band characteristics (Table 4; Fig. 5a–c). The O–H moiety of matrix might be preferentially interacted with N–H in a specific conformation thereby leading to the formation of a FT-IR peak with distinct free and bound N–H band appearance of chlorpheniramine maleate (Table 2b; Fig. 3c). Using microwave NDT technique, the nPAC values of films B1 obtained at the frequency bands of 8 and 12 GHz tend

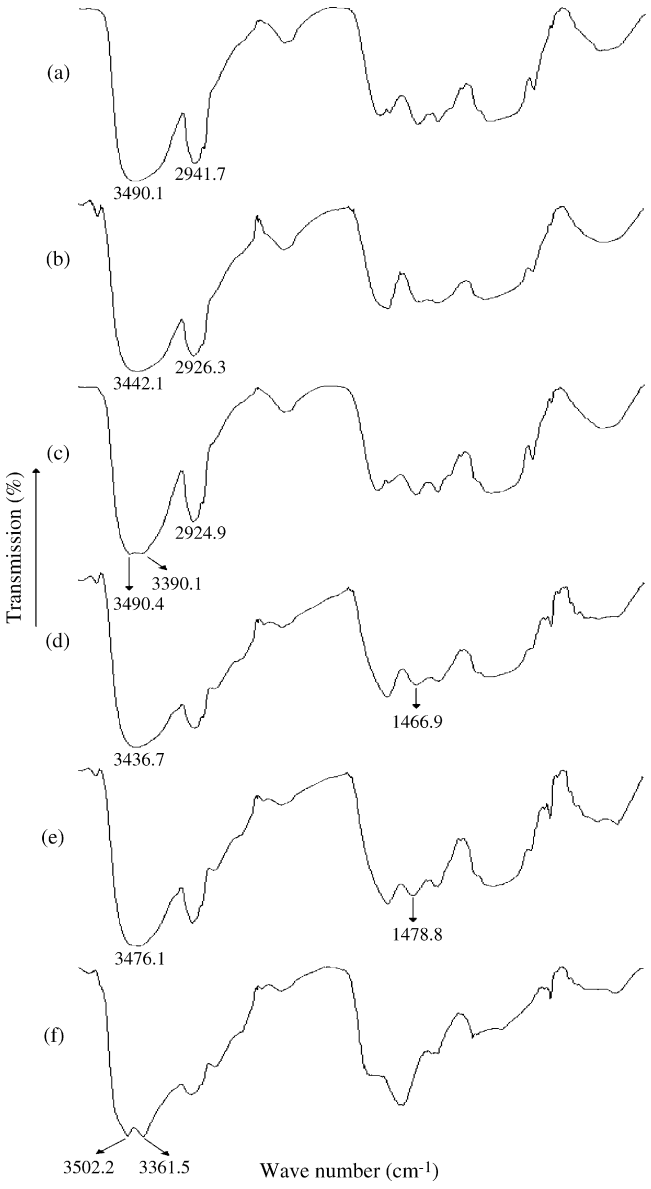

Fig. 5. FT-IR spectra of (a) B1: 25% RH, (b) B1: 50% RH, (c) B1: 75% RH, (d) B2: 25% RH, (e) B2: 50% RH and (f) B2: 75% RH.

to become larger with samples stored at a higher level of relative humidity (8 GHz—25% relative humidity: 0.23 ± 0.11%/mm; 50% relative humidity: 0.95 ± 0.21%/mm; 75% relative humidity: 44.91 ± 10.14%/mm; 12 GHz—25% relative humidity: 0.52 ± 0.34%/mm, 50% relative humidity: 8.69 ± 12.07%/mm, 75% relative humidity: 43.92 ± 8.56%/mm). Conversely, the nPTC values of the same samples became lower when films were stored under a more humid condition (8 GHz—25% relative humidity: 2338.27 ± 5.26%/mm; 50% relative humidity: 2323.03 ± 13.44%/mm; 75% relative humidity: 2268.63 ± 10.14%/mm; 12 GHz—25% relative humidity: 2327.23 ± 8.39%/mm; 50% relative humidity: 2304.32 ± 11.96%/mm; 75% relative humidity: 2269.44 ± 8.53%/mm). Similar trend was observed with respect to the relationship of nPAC and nPTC measurements of films B2 with the state of polymer–polymer and/or drug–polymer interaction in the matrix. In the case of films stored at a higher level of relative humidity, the FT-IR peak ascribing to C–H moiety was less visible, possibly due to the propagation of polymer–polymer and/or drug–polymer interaction involving the C=O, C–N and/or C=C of the aromatic ring in addition to that of the C–H functional group (Table 4; Fig. 5d–f). Generally, a lower propensity of polymer–polymer and/or drug–polymer interaction via the O–H/N–H and C–H moieties was noted when samples were stored at the relative humidity of 50% (Table 4; Fig. 5d–f). Using microwave NDT technique, the nPAC values of films B2 obtained at the frequency bands of 8 and 12 GHz were smaller with samples stored at the relative humidity of 50% (8 GHz—25% relative humidity: 57.80 ± 14.76%/mm; 50% relative humidity: 8.42 ± 6.13%/mm; 75% relative humidity: 66.87 ± 7.24%/mm; 12 GHz—25% relative humidity: 69.26 ± 15.91%/mm; 50% relative humidity: 24.10 ± 4.30%/mm; 75% relative humidity: 67.28 ± 4.43%/mm) whereas the nPTC values of the samples were larger when films were stored under the same condition (8 GHz—25% relative humidity: 1662.99 ± 14.75%/mm; 50% relative humidity: 1712.16 ± 6.12%/mm; 75% relative humidity: 1653.82 ± 7.23%/mm; 12 GHz—25% relative humidity: 1651.42 ± 15.83%/mm; 50% relative humidity: 1695.76 ± 4.36%/mm; 75% relative humidity: 1653.09 ± 4.40%/mm).

4. Conclusions

Blank HPMC film exhibited a greater propensity of polymer–polymer interaction at the O–H and C–H domains of the polymer chains upon storage at a lower level of relative humidity. In the case of loratadine loaded films, the polymer–polymer and/or drug–polymer interaction was propagated via the O–H moiety at a greater propensity in samples conditioned at the lower level of relative humidity, and via the C–H moiety when 50% relative humidity was selected as the condition for sample storage. Apparently, the absorption and transmission characteristics of both blank and drug loaded films for microwave varied with the state of polymer–polymer and/or drug–polymer interaction at O–H and C–H domains. The measurement of microwave NDT test at 8 GHz was sensitive to the chemical environment involving polar functional group such as O–H moiety while it was greatly governed by the less polar functional group such as C–H moiety in test conducted at the microwave frequency band of 12 GHz. Similar observation was obtained with respect to the profiles of microwave NDT measurements against the state of polymer–polymer and/or drug–polymer interaction of HPMC films carrying the chlorpheniramine maleate. Practically, the microwave NDT measurement is potentially suitable for use as an apparent indicator of the state of polymer–polymer and drug–polymer interaction of the matrix, in addition to the existing DSC and FT-IR techniques.

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