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Evaluation of methoxy polyethylene glycol-polylactide diblock copolymers as additive in hypromellose film coating

Marco Cespi[a], Luca Casettari[b], Giulia Bonacucina[a], Gianfabio Giorgioni[a], Diego R Perinelli[a] and Giovanni Filippo Palmieri[a]*

This paper deals with a new application of diblock methoxy polyethylene glycol-polylactide block copolymers, a class of synthetic biomaterials largely studied in the pharmaceutical and biomedical fields owing to their favorable properties such as biocompatibility, biodegradability, low immunogenicity, and good mechanical properties.

In this work, these materials were evaluated as additives for gastro-soluble pharmaceutical coating aimed to reduce film stiffness and water permeability. Two copolymers with different polylactide chain lengths were synthesized and characterized in term of molecular weight and solid-state properties. A series of free films with different hypromellose/copolymers ratio were prepared and characterized in terms of appearance, components miscibility, plasticity, and water vapor permeability.

The obtained results demonstrate that copolymers effectively influence hypromellose film properties according to their concentration and molecular weight. Specifically, the addition of the copolymer with a molecular weight of 6.5 kDa in a ratio hypromellose:polymer 5:1, allowed to obtain films with good appearance, improved plasticization, and water permeability properties. For higher molecular weight, copolymer or different ratios was not possible to observe the improvement of all the properties at the same time. The results also make possible to define the critical features to improve in order to use block copolymers as additive in hypromellose film coating.

The availability of new water-soluble additives able to work as plasticizer and moisture sealer in polymeric films represents an important progress not only in the field of pharmaceutical coating but also in that of food coatings, as for example in the formulation of edible films. Copyright © 2013 John Wiley & Sons, Ltd.

Supporting information may be found in the online version of this paper.

Keywords: hydroxypropyl methylcellulose (HPMC); mPEG-PLA diblock copolymers; differential scanning calorimetry (DSC); dynamic mechanical thermal analysis (DMA); water vapor permeability

INTRODUCTION

Block copolymers based on polyethylene glycol (PEG) as hydrophilic blocks, and α-hydroxy acids, such as polylactide (PLA), polycaprolactone, and polyglycolide as hydrophobic blocks, are synthetic biomaterials largely studied in the pharmaceutical and biomedical fields thanks to their favorable properties such as biocompatibility, biodegradability, low immunogenicity, and good mechanical properties.[1]

Up to now, these polymers have been successfully evaluated for several applications, such as the preparation of thermoresponsive hydrogels, nano or micro particles for controlled drug delivery, and building materials for the scaffold used to repair or replace diseased or damaged tissues. Wide collections of PEG-based copolymers applications are available in the literature.[1–6]

Another interesting feature of these copolymers is their film-forming ability. Such a characteristic has been exploited only to study their effect on the protein adsorption behavior[7] or to produce single layers inside multilayer membranes designed for wound healing applications.[8] So far, no research papers were published to evaluate PEG-based copolymers as main film-former component or as functionalized additive in the field of film coating for the preparation of pharmaceutical oral dosage forms, particularly for gastro-soluble coating.

Gastro-soluble coating is obtained using water-soluble (or soluble in low pH water medium) film-forming polymers, usually cellulose ethers (hypromellose, hydroxyethyl cellulose, or hydroxypropyl cellulose) or specific acrylic polymers (methacrylate amino ester copolymers), plasticizers, colorants, sealer, and other specific additives.[9] Currently, hypromellose represents the most commonly used polymers for the preparation of gastro-soluble coating,[10,11] and it is available on the market both as pure material to be formulated or ready-to-use products.

One of the major drawbacks of the gastro-soluble films is the high water permeability, which can affect the drug stability during the storage period of the dosage forms. The evaluation and the improving of water vapor permeability (WVP) of polymeric films, particularly those based on hypromellose (hydroxypropylmethyl cellulose or HPMC), has been the object of several investigations.

* *Correspondence to: Correspondence to: Giovanni Filippo Palmieri, School of Pharmacy, University of Camerino, Via Sant'Agostino n 1, 62032 Camerino Macerata, Italy. E-mail: gianfilippo.palmieri@unicam.it*

a *M. Cespi, G. Bonacucina, G. Giorgioni, D. R. Perinelli, G. F. Palmieri*
School of Pharmacy, University of Camerino, Camerino, Macerata, Italy

b *L. Casettari*
Department of Biomolecular Sciences, University of Urbino, Urbino, Pesaro e Urbino, Italy

polymers in advanced technologies

Results suggested that the use of hydrophilic additive generally increase the water permeability, whereas hydrophobic substances are reported to possess a variable effect,[12–17] probably depending on the chemical nature of the substances itself. However, hydrophobic additives can generate problems concerning disintegration and dissolution of the solid dosage forms.[9] Moreover, the presence of hydrophobic additives requires the preparation of suspensions instead of solutions.

Copolymers, made with hydrophilic and hydrophobic blocks, may represent interesting materials in the field of gastro-soluble coating. In fact, modulating the blocks' length and type, it could be possible to generate substances with intermediate water solubility, which can work both as plasticizers (the copolymer molecules have to be mainly molecularly dispersed in the main film-forming polymer chains) and as "moisture sealer", avoiding the concerns related to tablets disintegration and dissolution.

The aim of this paper is to evaluate the possible use of mPEG-PLA diblocks copolymers as additive in the formulation of hypromellose 2910 polymeric films. The addition of compound with tunable hydrophilic/hydrophabic behavior and possessing film-forming ability could be very useful to control the water permeability of hypromellose, the main film-former component.

In this work, two different copolymers were synthesized, keeping constant the mPEG block (5 kDa) whereas varying the PLA chain length, and they were used to prepare two different series of free HPMC films, each of them including different ratios of HPMC/mPEG-PLA. The obtained free films were analyzed in term of thermal, thermo-mechanical, and water permeation properties.

MATERIALS AND METHODS

Materials

Methoxy PEG (mPEG) Mw 5 kDa was purchased from Polysciences. 3,6-Dimethyl-1,4-dioxane-2,5-dione (L-lactide) was kindly donated by PURAC Biochem. Stannous-2-ethyl-hexanoate was purchased by Sigma-Aldrich. Hypromellose 50 cps (Methocel E50 premium LV, Colorcon, Dartford England) was supplied by Colorcon S.r.l. (Gallarate, Italy). All other reagents (Sigma-Aldrich) were standard reagent grade or higher and used without further purification.

Synthesis of block copolymers

$mPEG_{5000}$ (Polysciences GmbH, Eppelheim, Germany) (3 g) was added to a schlenk tube and melt at 80°C, under magnetic stirring and nitrogen atmosphere. Then L-lactide (1 or 2 g) was added into the flask increasing temperature to 150°C, respectively for copolymer A and B. Finally, a proper amount of the catalyst, stannous-2-ethyl-hexanoate, was added into the mixture, and the reaction was heated at 150°C for 2 hr (copolymer A) and 4 hr (copolymer B). Dichloromethane (3 ml) was added to the reaction mixture, and then the viscous solution poured into cold diethyl ether, under stirring, to precipitate the copolymers. The precipitated material was filtered and put under vacuum to remove any trace of solvents. The obtained powder was stored at +5°C for further investigations.

Characterization of the block copolymers

Proton nuclear magnetic resonance

Samples were dissolved in deuterium chloroform ($CDCl_3$) and the proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on a Bruker Advance 200 MHz spectrometer. Chemical shift values are reported in parts per million (δ) downfield from the internal standard tetramethylsilane (Me_4Si).

Gel permeation chromatography

A 7.5 mg of copolymer were solubilized into 1.5 ml of THF at 40°C for 1 hr. The solution was filtered with a regenerated cellulose syringe filter (0.45 μm pore size) and 7.5 μl di CH_3CN, the flow marker, was added. The analyses were carried out using a high performance liquid chromatography system (Agilent 1100 series), equipped with a gel permeation column (TSKGel 2500HHR from Tosoh Bioscience), kept at 35°C, and using THF as eluent with a flow rate of 1 ml/min. A calibration standard curve was achieved using a PEG calibration kit (PL2070-01000 by Varian) with molecular weight ranging from 106 to 21,300 M_p. Data were analyzed by the clarity software DATAAPEX (DataApex Ltd, Prague, Czech Republic).

Differential scanning calorimetry

Thermal analysis was carried out in a DSC 8500 (PerkinElmer, Norwalk, USA), equipped with an intracooler (Intracooler 2, PerkinElmer, Norwalk, USA) in an inert nitrogen atmosphere. A small amount (2–4 mg) of the samples was placed in a non-hermetically closed aluminum pan and analyzed, using an equal empty pan as reference. A typical two-stage program was used in heating the sample at 10°C/min from ambient temperature to 150°C in the first run and from −40°C to 210°C in the second run. The two cycles were separated by a cooling run at 10°C/min. The first heating stage was applied to remove the thermal history of the polymer (e.g. the processing and storage temperatures), whereas the second heating run gives data only related to the material, that is sample-specific.[18]

The instrument was calibrated following the manufacturer's procedure using indium and undecane as standards. All runs were performed at least in triplicate.

Preparation of free films

Water dispersion of hypromellose and diblock copolymers was prepared by mixing two different polymeric water dispersions, namely HPMC and copolymer solution.

"HPMC solution" was obtained dissolving hypromellose on water using the "hot/cold" technique.[19] The polymer was dispersed in two-thirds of the required amount of hot water (80°C), then adding the remaining amount of cold water, under magnetic stirring until a clear viscous solution was obtained. The solution was left at 5°C for at least 24 hr before further use. "HPMC solution" had a concentration equal to 4% w/w.

"Copolymer solutions" were prepared dissolving 0.15, 0.3, or 0.6 g of diblock copolymer in 5 g of water, adding then water to a final weight of 10 g, always under magnetic stirring. Also the "copolymer solutions" were left at 5°C for at least 24 h before further use.

37.5 g of "HPMC solution" and 10 g of "copolymer solutions" were mixed together in order to obtain a final solution having a hypromellose concentration equal to 3.2% and with a copolymer concentration varying from 0.32% to 1.26%. These concentrations determined a w/w ratio of hypromellose/copolymer equal to 5:0.5, 5:1, and 5:2.

The same procedure has been followed for both the synthesized copolymers.

Free films were obtained by casting the mixed solutions on a Petri dish, leaving them at ambient conditions until no decrease of weight was recorded. These procedures allowed to obtain dry polymeric disk with equal shape and similar thickness (186 μm ± 3%).

A control disk of pure hypromellose was prepared casting 47.5 g of 3.2% of a hypromellose solution following the same procedure.

Table 1 summarizes the different films prepared and their composition.

Characterization of free films

Thermal analysis of free films

Thermogravimetric analysis. The real water content of samples was determined by thermogravimetric analysis using an STA 6000 (PerkinElmer, USA). Approximately 5–20 mg of each of the prepared free films were placed in alumina crucibles, and the weight loss recorded from 25°C to 250°C at a rate of 10°C/min under nitrogen atmosphere.

All the tests were performed at least in triplicate.

Differential scanning calorimetry. Differential scanning calorimetry (DSC) analysis was performed following the same procedure previously reported.

Dynamic mechanical analysis. The thermo-mechanical properties of the free films were analyzed using a DMA 8000 (PerkinElmer, USA) equipped with a closed furnace. All the tests were performed in bending mode, using the dual cantilever geometry. The polymeric disks were cut into regular rectangular samples (9.5 × 20 mm) using a guillotine cutter specifically modified for this purpose, analyzed applying a constant deformation amplitude (15 μm) at a fixed frequency (1 Hz), and increasing the temperature from 25°C to 200°C at a scanning rate of 3°C/min.

All the tests were performed at least in triplicate.

Permeability analysis

Films WVP was determined using the permeability apparatus described by Obara and Kokubo.[11] The films were cut into disks and mounted between the gaskets of a holed lid with an air exposed surface area of 3.14 cm^2. The lid was tightly screwed on glass cups (3.59 cm diameter and 6.8 cm depth) containing 17 g of calcium chloride as desiccant. Cups were placed in a chamber containing a saturated sodium chloride solution (75% RH at 25°C), and their increase of weight was measured during a period of 6 weeks. Temperature during test was kept at 25°C.

The tests were performed for all the mPEG-PLA/HPMC films, using pure HPMC film as control. Moreover, two different controls: an open cup (without film) and a hermetically closed cup were also added. The open cup just needs to show the moisture sorption ability of the calcium chloride, whereas in the closed cup, it is necessary to correct the weight increase of all the samples, avoiding the influence of unrelated effects to the moisture sorption process.

Water vapor transmission rate and WVP were calculated as follows:

$$WVTR = \frac{dW}{dt} \cdot \frac{1}{A} \quad (1)$$

$$WVP = \frac{WVTR \cdot h}{\Delta p} \quad (2)$$

Where dW/dt is the slope of the variation in weight versus time plots (corrected by subtracting the film traces with this of the hermetically closed cup) calculated in the region of the steady state water vapor transfer by linear regression, A is the area of the exposed film surface, h is the film thickness, and Δp is the partial pressure difference through the film, calculated as follows:

$$\Delta p = S(R_1 - R_2)$$

Where S is the saturated vapor pressure at 25°C (3166 kPa), R_1 and R_2 are the relative humidity in the chamber and inside glass cups, respectively.

All tests were performed in triplicate, and the results reported as mean and standard deviation.

The WVP results for each molecular weight (Mw) series were compared against those of pure HPMC film by using the Dunnett's test (family error rate 0.1, individual error rate 0.0458 for Mw 9 kDa and 0.0619 for Mw 13 kDa).[20]

RESULTS AND DISCUSSION

Characterization of the block copolymers

The synthesized mPEG-PLA diblock copolymers were characterized by ^{1}H-NMR spectroscopy and by gel permeation chromatography (GPC). The ^{1}H-NMR spectra (Figure SF2 in supplementary materials) showed a peak at 5.2 ppm corresponding to the

Table 1. Name and composition of all the prepared films

Film name	Diblock copolymer	Hypromellose /Copolymer	Copolymer (%)	Hypromellose (%)	Copolymer (g)	Hypromellose (g)
HPMC	—	5:0	—	100	—	1.5
HyCo_A505	Copolymer A	5:0.5	9.1	90.9	0.15	1.5
HyCo_A510	Copolymer A	5:1	16.6	83.4	0.3	1.5
HyCo_A520	Copolymer A	5:2	28.6	71.4	0.6	1.5
HyCo_B505	Copolymer B	5:0.5	9.1	90.9	0.15	1.5
HyCo_B510	Copolymer B	5:1	16.6	83.4	0.3	1.5
HyCo_B520	Copolymer B	5:2	28.6	71.4	0.6	1.5

HPMC, hydroxypropyl methylcellulose

polymers in advanced technologies

methine PLA proton (−CH), a peak at 3.6 ppm for the protons of the repeating units in the mPEG chain ($-OCH_2$-CH_2), a peak at 3.4 ppm for the methoxy group of mPEG ($-OCH_3$), and a peak at 1.5 ppm for the methyl group of the PLA chain ($-CH_3$).

The ratio of the peak area at 1.6 and 3.4 ppm was indicative of the number of each repeating units (PLA and mPEG blocks, respectively and the number-average Mw of the synthesized copolymers.

Table 2 reports the Mw data, number-average (Mn) and weight-average Mw, polydispersity index (PDI), resulting from ^{1}H-NMR and GPC analysis of the synthesized polymers and the monomer mPEG. The polydispersity indexes of the copolymers were slightly higher than commercial monomer mPEG, indicating a well-performed synthetic process. According to GPC data, the two copolymers are formed by 105 units of ethylene glycol and 18 or 57 units of L-lactide, respectively.

The two copolymers and mPEG were analyzed by DSC in order to define the solid-state properties. All the materials showed a single endothermic transition (Figure SF2 in supplementary materials) identified as melting, with peak temperature and enthalpy dependent by the length of PLA chain (Table 2). The obtained results confirm the trend previously reported in the literature[21]: an increase of the PLA chain length on mPEG-PLA diblock copolymers showed a reduction of both melting temperature and enthalpy. No traces of amorphous material were detected, as indicated by the absence of glass transitions (Tg) at temperature lower than 40°C. DSC measurement performed on similar substances showed that they are mainly semi crystalline, with Tg temperatures at around 10–40°C.[21,22] This discrepancy appears to be related with the PEG/PLA ratio. In fact, the copolymers synthesized in the previously cited papers showed a clear predominance of the PLA block, whereas those synthesized here have a prevalence of the polyethylene oxide block.

Characterization of free films

All the free films were characterized by similar thickness and water content as reported in Table 3. The moisture percentages in the films were comparable with values reported in the literature for pure HPMC films.[23,24] However, after visual inspection, remarkable differences were observed comparing all the prepared films (Fig. 1). They showed different opacities and, above all, different homogeneity. Particularly, all the films containing the copolymer A, which had the lower Mw, were white and homogenous, except when the ratio hypromellose/copolymer was 5:2 (HyCo_A520). Concerning the samples prepared with the copolymer B, all the films showed an uneven appearance. They had a transparent whitish color, characterized by zones with different opacity. From the other side, pure hypromellose film was characterized by an excellent transparency and smooth surface, as previously reported.[25] Because of these results, it is possible to state that the films HyCo_A520, HyCo_B505, and HyCo_B510 do not possess the suitable appearance required for the coating of pharmaceutical dosage forms. Consequently, films with a ratio of hypromellose/copolymer higher than 5:2 and 5:1 for copolymer A and B, respectively, were not prepared.

Thermal analysis of free films

All the free films prepared were analyzed using DSC. This technique resulted to the ability to detect the copolymer melting,

Table 2. Molecular weight data and thermal properties of the synthesized copolymers and of the methoxy polyethylene glycol

Polymers	Molecular weight data				DSC data	
	Mn[a]	Mn[b]	Mw[b]	PDI[b]	Peak (°C)	ΔH (J/g)
mPEG	4727	4667	6007	1.29	63.3 ± 1.1	197.1 ± 4.3
Copolymer A	6500	5956	9071	1.52	57.4 ± 1.3	109.0 ± 5.5
Copolymer B	8400	8771	12957	1.47	56.4 ± 2.5	85.7 ± 4.7

DSC, differential scanning calorimetry; mPEG, methoxy polyethylene glycol; Mn, number-average; Mw, weight-average; PDI, polydispersity index
[a]Proton nuclear magnetic resonance
[b]Gel permeation chromatography
The results of differential scanning calorimetry are the mean ± standard deviation of three replicates

Table 3. Appearance, thickness and water content of the prepared films

Film	Color	Surface	Thickness (μm)	Water content (%)
HPMC	Transparent	Smooth	180 ± 5	4.8 ± 0.7
HyCo_A505	White	Smooth	185 ± 3	5.1 ± 0.6
HyCo_A510	White	Smooth	189 ± 5	3.5 ± 1.3
HyCo_A520	White	Slightly rough at upper side	192 ± 7	3.2 ± 0.2
HyCo_B505	Slightly whitish	Slightly rough at upper side	182 ± 5	4.8 ± 1.2
HyCo_B510	Transparent	Slightly rough at upper side	190 ± 6	4.3 ± 0.6

HPMC, hydroxypropyl methylcellulose.
The results of thermogravimetric analysis are the mean ± standard deviation of three replicates, while thickness values are the mean ± standard deviation of three measures in three different points of each film.

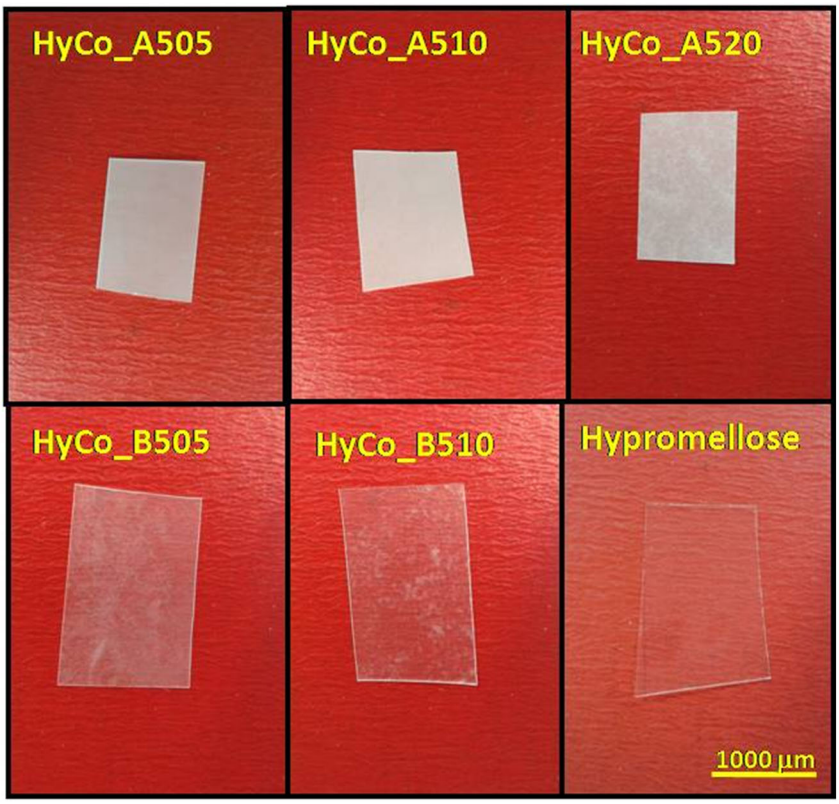

Figure 1. Pictures of all the prepared free films. This figure is available in color online at wileyonlinelibrary.com/journal/pat

whereas it showed low resolution concerning the HPMC Tg at around 150–170°C[23,24,26] (Figure SF3 in supplementary materials). The presence of the copolymers melting peaks on DSC traces suggests that these materials are not completely dispersed in the films, thus the analysis of melting transitions of copolymers allows to study the effect of HPMC matrix on the crystallinity of mPEG-PLA.

The melting temperature of the copolymers in the hypromellose films are reported in Table 4. It is possible to observe that the melting point of copolymers increases as their amount in the film grows, almost approaching the value of the pure materials. Because the mPEG-PLA melting point differences recorded between the film samples and also between the films and pure materials are at maximum around 2.5°C, the copolymers crystalline structures inside the HPMC matrices should be very similar to each other and also to those of the starting materials.

The analysis of melting point transitions allows also to quantify the amount of crystalline copolymer, which represents the amount of copolymer not homogeneously dispersed in the hypromellose films. The weight of crystalline copolymer for each film was calculated from DSC thermogram, according to the following equation:

$$\mathrm{Wcc\ (gr)} = \frac{h_{melt}}{\Delta H_{melt}} \tag{3}$$

Where h_{melt} is the area of the mPEG-PLA melting transition on the DSC traces of the films, whereas DH_{melt} is the melting enthalpy determined from DSC of the pure copolymer (Table 2).

Table 4. Thermal properties of the prepared films

Film	Mp (°C)[a]	CDD (%)[a]	Tg at 1Hz (°C)[b]
HPMC	—	—	171.5 ± 0.7
HyCo_A505	54.9 ± 0.8	64.9 ± 0.6	157.0 ± 3.4
HyCo_A510	55.7 ± 0.3	44.9 ± 2.9	156.1 ± 1.2
HyCo_A520	56.7 ± 0.4	33.0 ± 4.4	152.9 ± 1.8
HyCo_B505	53.9 ± 0.5	55.2 ± 3.8	157.7 ± 0.7
HyCo_B510	54.9 ± 0.1	48.2 ± 0.5	156.6 ± 1.9

Mp, Copolymers melting temperature; CDD%, percentage of copolymers dispersion degree; Tg, hypromellose glass transition temperature
[a]Determined by differential scanning calorimetry
[b]Determined by dynamic mechanical thermal analysis
All the data are the mean ± standard deviation of three replicates.

polymers in advanced technologies

From the total weight of the analyzed films and the total amount of copolymer in the film, the percentage of crystalline mPEG-PLA can be calculated from the weight of crystalline copolymer calculated from Equation 3.

All the non-crystalline copolymers in the film represent the copolymer dispersion degree (CDD %) and could be considered as an estimation of the "solid-state affinity" of the mPEG-PLA in the hypromellose matrix. The results (Table 4) showed a clear correlation of the CDD % with the amount of copolymer in the films. Obviously, the higher values of CDD were found with the lowest amount of the mPEG-PLA, that is 65% and 55% for the copolymer A and B, respectively. The copolymer increment inside the HPMC matrix leads to a clear reduction of these values up to a minimum CDD value of 33% in the film HyCo_A520.

Differential scanning calorimetry allowed to analyze the effect of HPMC matrix on the solid-state properties of copolymers. However, to study the opposite effect, that is that of the copolymers on hypromellose films, it is necessary to use a technique more sensitive to low energy transitions, such as Tg. For this reason, the prepared films were analyzed also using a dynamic mechanical analyzer. The effect of copolymer type and concentration on the Tg temperature of hypromellose films represent one of the most common procedure to evaluate their plasticizing effect. In dynamic mechanical analysis, traces of the Tg is represented by a step in the storage modulus or as a peak in the tangent of the phase angle (tan d) (Fig. 2). The Tg values, calculated as the peak of the tan d traces, are reported in Table 4. Data clearly show a reduction of the hypromellose Tg as the copolymers concentration increases, whereas the copolymer type do not appear to have any influence, at least in the range of PLA chain lengths prepared. The reduction of Tg temperature suggests that these copolymers effectively possess a plasticizing effect. The films plasticization results comparable with those of the commercially "ready-to-use" hypromellose-based films, where the reduction of Tg was approximately of 10–30°C with respect to the value of pure hypromellose films.[27]

Permeability analysis

The water permeability is a very important feature in gastrosoluble coating because it represents the ability of films to protect the inner core from the moisture effects.

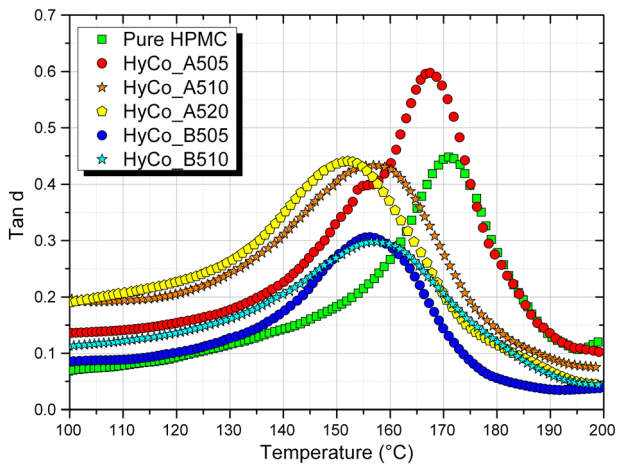

Figure 2. Dynamic mechanical analysis traces of the prepared free films. This figure is available in color online at wileyonlinelibrary.com/journal/pat

The weight increase of the permeability cup against the time is showed in Fig. 3 for all mPEG-PLA films and the control (pure HPMC film). Moreover, it also showed the weight increase of open cup. By comparing the plots, the effect of the different film compositions on water permeability is evident. All the samples with the lowest hypromellose/copolymer ratio (5:0.5) showed similar weight gain and almost superimposed traces when compared with control film (Fig. 3). On the other hand, films prepared with higher hypromellose/copolymer ratio were much more performing in reducing the water permeability, being able to decrease it up to 50% compared with the values of pure hypromellose film.

The weight increase plots allow a rough comparison among different formulations; however, they do not take into account the different thickness of the films. For this reason, a more rigorous manner to analyze the permeation data is to calculate the WVP. WVP results (Fig. 4) confirm the general trend observed on the weight increase-time plots. The WVP value of pure

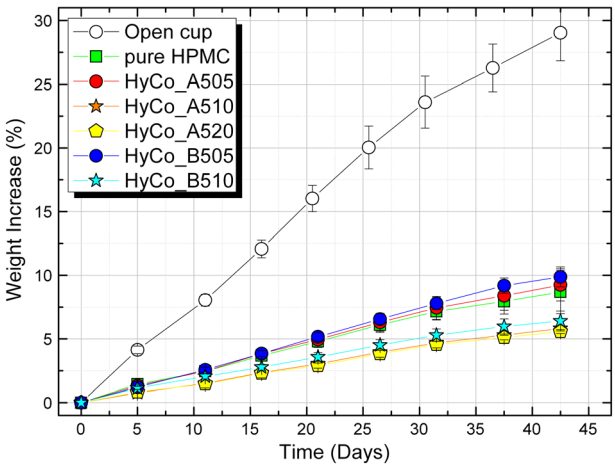

Figure 3. Increase of weight versus time of all the prepared free films recorded during the permeability tests. All the data are the mean ± standard deviation of three replicates. This figure is available in color online at wileyonlinelibrary.com/journal/pat

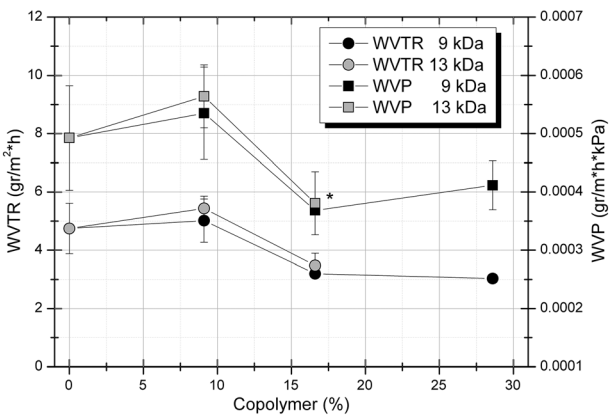

Figure 4. Effect of copolymer type and concentration on the water vapor transmission rate and water vapor permeability of hydroxypropyl methylcellulose (HPMC) films. All the data are the mean ± standard deviation of three replicates. The asterisks *(Mw 9 kDa) and the hashes #(Mw 13 kDa) indicate samples with water vapor permeability statistically different from that of pure HPMC film according with the Dunnett's test.

hypromellose film is comparable with those previously reported in the literature,[25] and it is reduced by the addition of the copolymers. Particularly, the WVP reduction was dependent by the mPEG-PLA concentration, although only the sample HyCo_A510 gave differences statistically relevant. The trends observed in Fig. 4 appear dependent on the amount of amorphous copolymer inside the films, which is due to the total amount of copolymer and to the CDD. Specifically, the total amount of amorphous copolymer is 5.9 ± 0.1, 7.5 ± 0.5, and 9.4 ± 1.3 for the films containing the 9 kDa series, following more or less the WVP trends on Fig. 4. Same considerations can be done for films containing the 13 kDa series, even if in this case, the ratio 5:2 was not analyzed.

On the contrary, the PLA chains length of the copolymer do not show any relevant influence on WVP, at least in the Mw range of the synthesized copolymers.

Thus, these results highlighted the importance of copolymers Mw and solid miscibility with the main film-former component. This last aspect appears critical and should be improved during the planning of the synthetic step.

CONCLUSION

This study evaluated for the first time the incorporation of mPEG-PLA diblocks copolymers into hypromellose films. The obtained results showed that these materials are able to modify the properties of HPMC films in term of appearance, plasticization, and WVP. The improvement of WVP is particularly relevant since it was obtained with water-soluble substances, whereas at the moment, it is usually reduced by using only insoluble additives.

The copolymers' efficiency was always dependent by the concentration, while the PLA chain length influenced only the film appearance and homogeneity. Taking into account the film properties required in the field of pharmaceutical coating, only the low Mw copolymer added into the hypromellose film at a concentration equal to 16.6% resulted effectively performing as coating additive.

From the results, it is evident that Mw and hydrophilicity/hydrophobicity ratio play a fundamental role in the copolymers performance. These chemical features are related to the copolymers solid miscibility with HPMC. High miscibility appeared to be a critical feature for the whole performance of multi-component films, especially when more polymeric materials are present.

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