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Research paper

Importance of glassy-to-rubbery state transitions in moisture-protective polymer coatings

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ABSTRACT

The aim of this study was to better understand the mechanisms governing water transport in polymeric film coatings used for moisture protection. Tablets containing garlic powder were coated with Methocel® E5 (hydroxypropyl methylcellulose), Opadry® AMB [poly(vinylalcohol)-based formulation] and Eudragit® E PO [poly(methacrylate-methylmethacrylate)]. Their water content at different temperatures and relative humidities were determined. The polymers were characterized by X-ray powder diffraction and differential scanning calorimetry (DSC). The latter revealed significant physical changes in Opadry® AMB during storage, while Eudragit® E PO remained unchanged. For Opadry® AMB, a strong dependence of the vapor permeability on the water content of the system was observed. The water uptake drastically increased with increasing relative humidity and storage temperature due to structural polymer changes (glassy-to-rubbery state transition). Linear relationships between the initial uptake rate and the relative humidity or temperature were established. Storage below critical threshold values of 66% RH (at room temperature) and 16 °C (at 75% RH) significantly reduced water imbibition. Opadry® AMB-based film coatings undergo a glassy-to-rubbery state transition upon storage at room temperature and elevated relative humidity, resulting in significantly increased mobility of the polymer chains and, thus, increased water uptake rates.

1. Introduction

Moisture-protective polymer coatings are often used to prolong the storage stability of water-sensitive drugs, including many herbal extracts [1–3]. The thickness of this barrier coating (coating level) and its composition (determining the mobility of water molecules) strongly affect the moisture permeability of the coatings. Commonly used film-formers for moisture-protective polymer coatings include hydroxymethylcellulose (HMC), hydroxypropyl methylcellulose (HPMC), poly(vinylalcohol) (PVA), ethylcellulose, shellac and poly(methacrylate-methylmethacrylates) [4–10]. Recently, the influence of coating and curing conditions on water penetration kinetics has been studied [11].

Little knowledge is available on the importance of the physical state of the macromolecules in moisture-protective polymer coatings. The macromolecules can either be in the crystalline or be in the amorphous state. An amorphous polymeric network can be either in the glassy or in the rubbery state, depending on its glass transition temperature. In other areas of pharmaceutical sciences, the importance of glassy-to-rubbery state transitions of polymeric excipients has been extensively studied [12,13]. The main physicochemical parameter used to characterize amorphous polymers is the glass transition temperature (Tg). This is the temperature at which an amorphous substance in the glassy state is transformed into the rubbery state, resulting in rearrangement of the molecules into a new, higher energetic structure. This transition is mainly induced by a change in temperature. The glassy-to-rubbery state transition and other thermal events can be detected by differential scanning calorimetry (DSC), which involves the application of a constant heating or cooling signal to a sample and the subsequent measurement of the total heat flow response [14,15]. Sinusoidal modulation of the heating or cooling signal offers the advantage to differentiate the total heat signal into a reversing and a non-reversing heat flow (modulated temperature DSC = MTDSC). This technique allows the determination of Tgs in the reversing signal while separating the overlapping irreversible thermal events like exothermic relaxation peaks in the non-reversing response [16–18]. A glass transition is observed in all amorphous materials and in partially crystalline polymers containing amorphous regions. The glass transition temperature is mainly controlled by the polymer itself. Polymers containing bulky side groups generally exhibit higher Tg values than polymers without bulky side groups [19]. In a series of homologous polymers, the glass transition temperature increases with increasing molecular weight [20].

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Materials in the amorphous state have a higher capacity for moisture sorption than in the crystalline state [21]. The uptaken water may be thought of as “dissolving” into the amorphous structure and acting as a plasticizer [22]. Consequently, the glass transition temperature of the polymeric system decreases with increasing water content. The Gordon Taylor equation can be used to quantitatively describe this phenomenon [23]. Obviously, the role of water acting as a plasticizer is of major importance for understanding the effects of moisture on the physical properties of solid dosage forms. A moisture-induced reduction of the Tg to a level near or below the operating temperature can be sufficient to induce re-crystallization of low-molecular-weight substances during pharmaceutical processing [24]. Consequently, the Tg of polymeric systems used for moisture protection plays a fundamental role in their performance. State transitions of the macromolecules can result in drastically increasing water vapor permeability through protective film layers. The effects of the presence of different types of plasticizers in polymeric coating formulations have been reported in the literature [25–27]. Moisture permeates more rapidly through films containing hydrophilic plasticizers [28], whereas the addition of hydrophobic plasticizers showed no major impact [29]. Anti-plasticizers resulted in an increase in the glass transition temperature, if the polymer and plasticizer were intimately mixed [30,31].

The aim of the present study was to better understand the moisture-protective ability of polymeric film coatings. Freeze-dried garlic powder was used as a moisture-sensitive drug, which was compressed into tablets. The tablets were coated with different types of polymers, and the resulting water uptake kinetics during storage at different temperatures and relative humidities were monitored. X-ray powder diffraction and differential scanning calorimetry were used to characterize the physical state of the macromolecules and changes thereof during storage. As the stability of the herbal drug garlic powder strongly depends on the water content of the systems, the latter was used as an indicator for storage stability.

2. Materials and methods

2.1. Materials

The following materials were used as received: tablets containing 100 mg freeze-dried garlic powder (diameter: 8 mm, weight: 250 mg) (Lichtwer-Pharma, Berlin, Germany); poly(methacrylate-methylmethacrylate) copolymer (Eudragit® E PO, Degussa, Darmstadt, Germany); hydroxypropyl methylcellulose (Methocel® E5 Colorcon, Orpington, UK); partially hydrolyzed poly(vinylalcohol) (Opadry® AMB white, Colorcon); poly(vinylpyrrolidone) (PVP, Kollidon® 90; BASF, Ludwigshafen, Germany); poly(vinylpyrrolidone)vinylacetate (PVPVA, Kollidon® VA64; BASF); triethyl citrate (TEC; Morflex, Greensboro, USA).

2.2. Tablet coating

Tablets were coated in a pan coater (15 rpm, air flow rate: 130 m^3/h, nozzle diameter: 1.2 mm, spraying pressure: 1.3 bar; Glatt® GC-300, Glatt, Binzen, Germany). Aqueous solutions or dispersions of the investigated polymers (7–25% w/w) were sprayed onto pre-heated tablets under the specific conditions recommended by the manufacturers (Table 1) until a coating level of 10% (w/w) was reached. TEC (10% w/w, based on the polymer) was added as plasticizer to Methocel® E5. Optionally, the tablets were cured upon coating in a drying chamber (Heraeus T6120, Heraeus, Hanau, Germany) for 1, 3 or 24 h (as indicated).

Table 1
Coating conditions for the investigated polymers according to the recommendations of the respective manufacturers.

Formulation	Polymer concentration % (w/w)	Inlet air temperature (°C)	Outlet air temperature (°C)	Spraying rate (g/min)
Methocel® E5	7	60	40	4.2
Opadry® AMB	15	65	43	7.5
Eudragit® E PO	9	45	30	7.3

2.3. Preparation of thin polymeric films

Solutions/dispersions of Eudragit® E PO, Methocel® E5 and Opadry® AMB in demineralized water (10% w/w) were cast into teflon molds (10 cm × 10 cm) and subsequently dried at 60 °C in a drying chamber (Heraeus T6120) for 24 h. The thickness of the dried films was approximately 300 μm.

2.4. Water uptake studies

The water content (in percentage, w/w) of tablets before storage was determined as mass loss upon drying at 105 °C in a drying chamber (Heraeus T6120) for 3 h [water content (%) (t_0)] ($n = 2$). Tablets were openly stored at different temperatures (2–37 °C) and/or relative humidities (RHs) [in closed desiccators containing saturated solutions of $NaNO_3$ (72.3% RH), NaCl (74.4% RH), $ZnSO_4$ (84.9% RH), $CuSO_4$ (97.9% RH), pure H_2O (100.0% RH), determined with a digital hygrometer (Rotronik® A1H, Rotronik, Bassersdorf, Switzerland)]. At predetermined time intervals, samples were withdrawn and accurately weighted [$m(t)$]. The water content (in percentage, w/w) as a function of time t was calculated as follows:

$$\text{water content } (\%)(t) = \frac{m_{\text{water}}(t)}{m(t)} \cdot 100\% \quad (1)$$

$$m_{\text{water}}(t) = \text{water content } (\%)(t_0) \cdot m(t_0) + m(t) - m(t_0) \quad (2)$$

where $m_{\text{water}}(t)$ denotes the amount of water in the sample at time t; $m(t_0)$ and $m(t)$ represent the total weight of the tablets at time $t = 0$ and t, respectively ($n = 3$).

Zero-order water uptake rate constants were determined from the linear portions of the water content versus time profiles (early time points) by linear regression.

The water uptake of the polymeric coatings was determined by peeling off the coatings from the tablets at predetermined time points and by measuring their water contents as mass loss on drying at 120 °C for 90 min using a thermobalance (Mettler® TG 50, Mettler, Giessen, Germany).

2.5. Differential scanning calorimetry (DSC)

DSC studies were performed using a Mettler® DSC 821e (Mettler) coupled to a TA-controller (Mettler® TC 15, Mettler). Samples (4–10 mg) were weighed in 40 μl aluminum pans and closed (for measurements above 100 °C, a pinhole was introduced into the lid). Standard DSC scans were recorded for Opadry® AMB- and Eudragit® E PO-based formulations (heating rate = 3 K/min), whereas modulated temperature DSC (MTDSC) was used to characterize Methocel® E5-based formulations (time period = 60 s, heating rate = 1 K/min, amplitude = 1 K). The cell was purged with 80 ml/min nitrogen. Polymeric coatings were peeled off from the tablets at predetermined time points during open storage at 75% RH and room temperature and measured.

2.6. X-ray powder diffraction

Wide angle X-ray scattering measurements were performed on a Philips PW 1830 X-ray generator with a copper anode (Cu Kα radiation, γ = 0.15418 nm, 40 kV), fixed with a Philips PW 1710 diffraction control unit (Philips Industrial & Electro-acoustic Systems Divisions, Almelo, the Netherlands). The radiation scattered in the samples was measured using a vertical goniometer (Philips PW 1820, Philips Industrial & Electro-acoustic Systems Divisions). Patterns were obtained with a step width of 0.02° and a detector in 2θ between 4° and 40° at ambient temperature.

3. Results and discussion

3.1. Water uptake kinetics during storage at 75% relative humidity

Very different rates and extents of water uptake were observed for tablets (containing 100 mg garlic powder) coated with Methocel® E5 (a low viscosity HPMC type 2910 USP), Opadry® AMB [a poly(vinylalcohol)-based coating formulation], or Eudragit® E PO [a poly(methacrylate-methylmethacrylate)-based coating formulation] during open storage at room temperature and 75% RH (Fig. 1).

Tablets coated with Methocel® E5 showed the highest water uptake rates at early time points (up to 1.46%/d). This can be attributed to the relatively high hydrophilicity of HPMC and its significant swelling capacity compared to the other two polymers. The water uptake rate monotonically decreased to 0.07%/d, which can be attributed to the increased water content and equilibration of the tablets and, thus, decreased concentration gradients (being the driving force for diffusion) (Fig. 2A).

Eudragit® E PO-coated tablets showed much slower water uptake kinetics than Methocel® E5-coated tablets, indicating a lower water vapor permeability of Eudragit® E PO-based coatings (Figs. 1 and 2B). This polymer is a promising candidate for moisture-protective coatings.

Tablets coated with Opadry® AMB showed a completely different water uptake behavior compared to Eudragit® E PO- and Methocel® E5-coated systems (Figs. 1 and 2). The initial water uptake rate was very low (0.09%/d) and then – in contrast to the other two polymer coatings – increased with time, reaching a maximum of 0.44%/d at 8 d. Afterwards, the water uptake rate decreased. The initial increase in the uptake rate is likely to be attributable to structural changes within the polymeric networks, caused by the water influx into the system. The subsequent decrease in the water uptake rate can probably be explained by the increase in the water content of the system, resulting in decreased concentration gradients. In this study, Opadry® AMB-based coatings showed the lowest water uptake rates of the three investigated coating

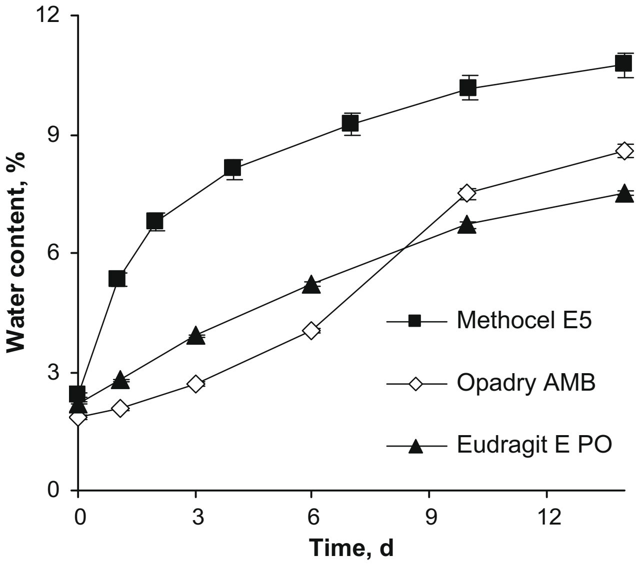

Fig. 1. Water uptake kinetics of coated tablets containing 100 mg garlic powder during open storage at 75% RH and room temperature (the type of polymer coating is indicated in the figure).

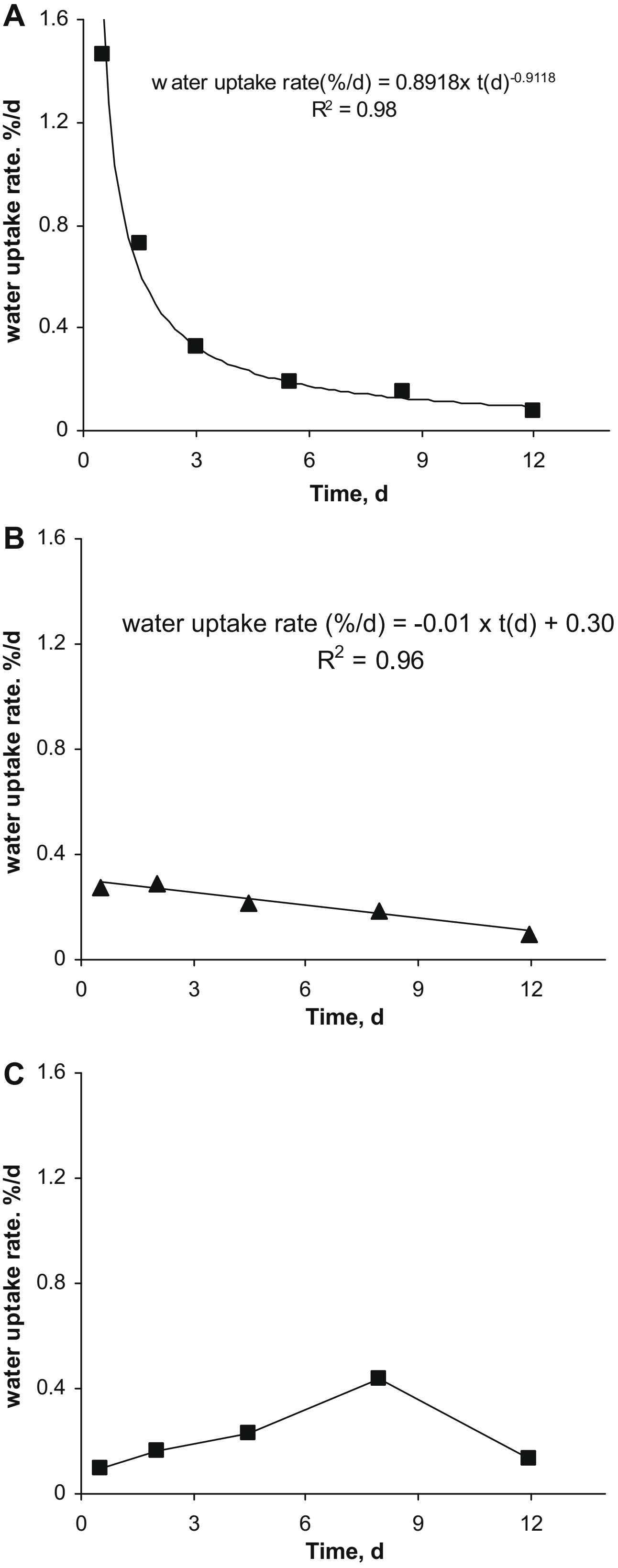

Fig. 2. Water uptake rates of tablets containing 100 mg garlic powder coated with (A) Methocel® E5, (B) Eudragit® E PO and (C) Opadry® AMB during storage at 75% RH and room temperature.

formulations before the onset of these structural changes. Thus, it offers an interesting potential for moisture-protective coatings.

To better understand the reasons for the significant differences in the shape of the water uptake curves of the three investigated formulations, in particular the sudden change in the penetration rate in the case of Opadry® AMB-coated tablets, the physical state of the polymeric coatings before and upon open storage at 75% RH was studied using X-ray powder diffraction and differential scanning calorimetry.

3.2. Physical state of the polymeric matrices

Eudragit® E PO and Methocel® E5 are amorphous polymers; their physical state was not affected by storage at room temperature and 75% RH for 5 d and the resulting water uptake (Fig. 3A). In contrast, the X-ray patterns of Opadry® AMB showed clear diffraction peaks at 9, 19, 25, 29 and 38° (2θ) before and after storage at elevated relative humidity, indicating crystalline structures in this coating formulation. The peaks at 9, 19, 25 and 29° (2θ) could be attributed to the presence of talcum, and the peaks at 25 and 38 (2θ) to the presence of titan dioxide in the formulation (Fig. 3B). Thus, they do not allow any conclusion on the physical state of the polymer [poly(vinylalcohol)] in Opadry® AMB.

In addition, differential scanning calorimetry (DSC) was used to study the physical state of free polymeric films (of identical composition as the coating formulations) before and after storage at room temperature and 75% RH. The Tg of Eudragit® E PO and Opadry® AMB films decreased with increasing storage time (Table 2)

Table 2
Changes in the glass transition temperature (Tg) of free polymeric films (of identical composition as the coating formulations; determined by differential scanning calorimetry) before and after storage at 75% RH and room temperature (“–”: not measured).

Storage time (d)	Tg (°C)		
	Methocel® E5	Eudragit® E PO	Opadry® AMB
0	159	54.2	52.1
1	166	53.6	26.3
1.75	–	53.4	24.7
3	–	51.6	22.5
5	–	50.0	20.8
14	167	46.7	17.6

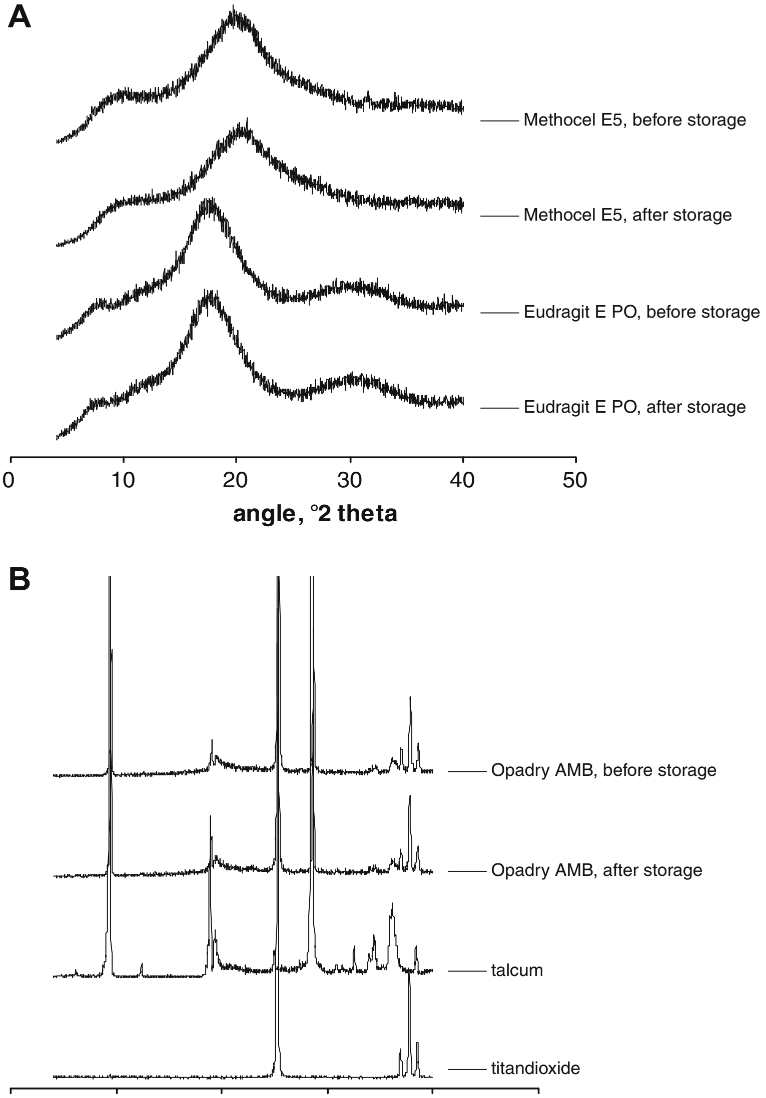

Fig. 3. X-ray diffraction patterns of (A) Methocel® E5 and Eudragit® E PO and (B) Opadry® AMB before and after storage at 75% RH and room temperature for 5 d, as well as of talcum and titandioxide.

because of the plasticizing effect of water. The Tg of Eudragit® E PO remained above room temperature, indicating that this polymer was in the glassy state throughout storage. This explains the observed low water permeability of Eudragit® E PO-based coatings (Fig. 1): The mobility of the macromolecules is much lower in the glassy state than in the rubbery state. According to the free volume theory of diffusion, this results in lower probabilities for a water molecule to jump from one cavity to another and, thus, to reduced water vapor penetration rates [32].

In contrast, the glass transition temperature of Opadry® AMB was initially above room temperature (52.1 °C) and then decreased to 17.6 °C after 14 d exposure to 75% RH. Thus, the polymer underwent a glassy-to-rubbery state transition. The mobility of the macromolecules increased and, thus, the permeability of water vapor increased. This effect dominated at early time points and explains the observed initial increase in the water uptake rate of coated tablets (Fig. 2C). However, as with Eudragit® E PO- and Methocel® E5-based coatings, the water content of the tablets increased with time, resulting in decreased water concentration gradients and, thus, decreased penetration rates (Fig. 2C).

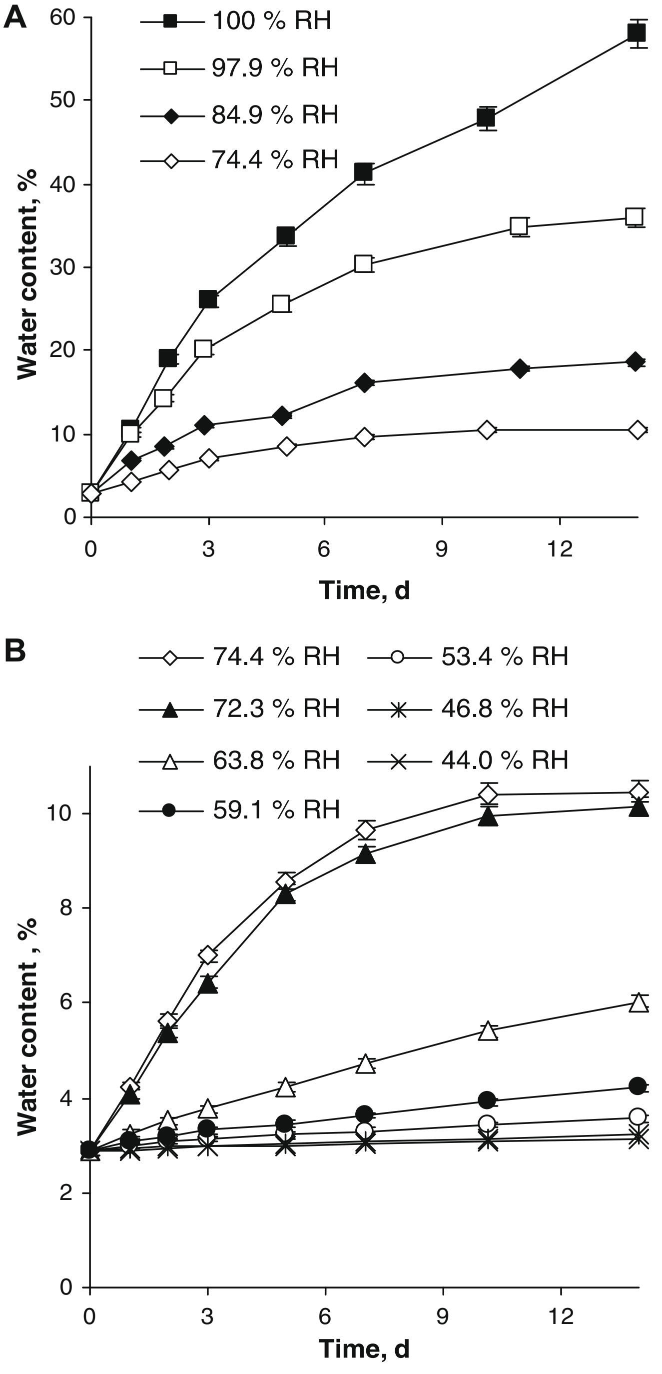

Fig. 4. Water uptake kinetics of tablets containing 100 mg garlic powder coated with Opadry® AMB during open storage at different relative humidities (at room temperature): (A) 100–74.4% RH and (B) 74.4–44.0% RH (please note the different scaling of the water content-axes).

The Tg of Methocel® E5-based films was 159 °C before storage at 75% RH and remained in this order of magnitude during the observation period (Table 2).

3.3. Glassy-to-rubbery state transition in Opadry® AMB-based coatings

To better understand the glassy-to-rubbery state transition in Opadry® AMB-based coatings, the water uptake kinetics of coated tablets were monitored during open storage at different relative humidities (Fig. 4) and temperatures (Fig. 5). An increase in storage humidity from 44.0% to 100% led to a drastic increase in the water uptake rate and extent (at constant temperature = room temperature). This can be explained by the higher equilibrium moisture content at higher humidity and the plasticizing effects of water. The water penetration clearly increased when increasing the relative humidity from 59.1% to 72.3% (Fig. 4B), indicating potential structural changes in the polymeric coatings, e.g., a glassy-to-rubbery state transition.

The water uptake rate of Opadry® AMB-coated tablets stored at constant relative humidity (75% RH) increased with increasing temperature (Fig. 5). This was attributed to the increasing mobility of the macromolecules with increasing temperature [32], resulting in increased water molecule mobility in the polymeric coatings. A pronounced acceleration of the water penetration was observed between 12 and 23 °C, again indicating potential structural changes in the polymeric systems (e.g., a glassy-to-rubbery state transition).

Fig. 6A and B illustrates the dependence of the water uptake rate of Opadry® AMB-coated tablets (at early time points) on relative humidity (at constant temperature) and on temperature (at constant relative humidity) during storage. Linear relationships

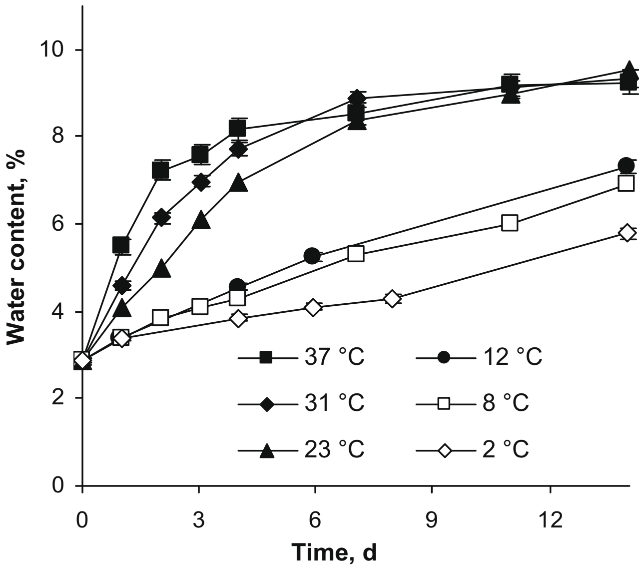

Fig. 5. Water uptake kinetics of tablets containing 100 mg garlic powder coated with Opadry® AMB during open storage at different temperatures (at 75% RH).

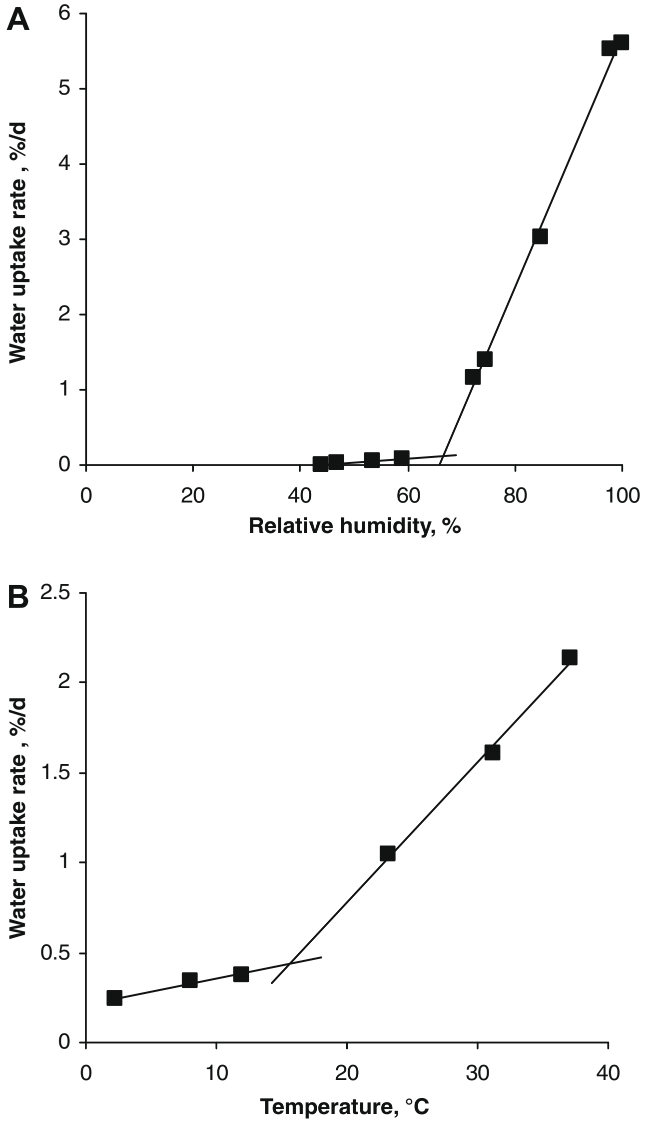

Fig. 6. Dependence of the water uptake rate (at early time points) of Opadry® AMB-coated tablets containing 100 mg garlic powder on (A) the relative humidity (at room temperature) and (B) temperature (at 75% RH) during storage. The symbols represent the experimentally determined water uptake rates, the straight lines fitted linear equations (Eqs. (3)–(6)).

were observed between (i) the water uptake rate and relative humidity (RH) and (ii) the water uptake rate and temperature (T):

$$\begin{aligned}&22\text{–}59.1\%\ \text{RH}\quad \text{water uptake rate}\ (\%/\text{d})\\&\quad = 0.0045 \cdot \text{RH}\ (\%) - 0.188, \quad R^2 = 1.00 \qquad (3)\end{aligned}$$

$$\begin{aligned}&72.3\text{–}100\%\ \text{RH}\quad \text{water uptake rate}\ (\%/\text{d})\\&\quad = 0.1671 \cdot \text{RH}\ (\%) - 11.011, \quad R^2 = 1.00 \qquad (4)\end{aligned}$$

$$\begin{aligned}&2\text{–}12\ ^\circ\text{C}\quad \text{water uptake rate}\ (\%/\text{d})\\&\quad = 0.0142 \cdot T\ (^\circ\text{C}) + 0.2149, \quad R^2 = 0.96 \qquad (5)\end{aligned}$$

$$\begin{aligned}&23\text{–}37\ ^\circ\text{C}\quad \text{water uptake rate}\ (\%/\text{d})\\&\quad = 0.0776 \cdot T\ (^\circ\text{C}) - 0.7686, \quad R^2 = 1.00 \qquad (6)\end{aligned}$$

Interestingly, in both cases (Fig. 6A and B), two linear regions could be distinguished (as indicated in the diagrams). The interceptions of the respective straight lines represent (i) the critical relative humidity at room temperature (Fig. 6A) and (ii) critical temperature at 75% RH (Fig. 6B), at which the glassy-to-rubbery state transition occurs. Thus, the properties of the polymeric systems fundamentally change at 66% RH (and room temperature) and at 16 °C (and 75% RH). Consequently, the water uptake of Opadry® AMB-coated tablets can be expected to be low during storage below 66% RH at room temperature and below 16 °C at 75% RH.

Next, the Tg of Opadry® AMB powder equilibrated at different RHs was determined by DSC analysis in order to verify the hypothesis that the abrupt changes in the water uptake rates were caused by a glassy-to-rubbery state transition (Fig. 7). The glass transition temperature linearly decreased with increasing RH because of the plasticizing effect of water (the water content of Opadry® AMB increased with increasing RH). A linear relationship between the Tg and RH could be established:

$$\text{Tg}\ (^\circ\text{C}) = -0.667 \cdot \text{RH}\ (\%) + 66.5, \quad R^2 = 0.99 \qquad (7)$$

The two conditions for the glassy-to-rubbery state transition of Opadry® AMB, which were hypothesized based on the observed water uptake kinetics of coated tablets (room temperature and 66% RH as well as 16 °C and 75% RH), agreed very well with the DSC measurements. The respective Tg–RH data points overlap with the straight line (Fig. 7). This clearly shows the fundamental importance of glassy-to-rubbery state transitions in polymeric film coatings used for moisture protection.

3.4. Addition of anti-plasticizing agents to the polymeric coatings

Opadry® AMB was selected for further studies because it showed the most promising moisture-protective ability of the investigated polymer coatings as long as it was in the glassy state (Fig. 1). The idea was to avoid/delay the onset of the glassy-to-rubbery phase transition during storage in order to minimize water uptake rates and extents. Different amounts of two anti-plasticizing agents [poly(vinylpyrrolidone) (PVP) and poly(vinylpyrrolidone)vinylacetate (PVPVA)] were added to Opadry® AMB in order to increase the Tg of the polymeric coatings, avoiding/delaying the decrease below room temperature during storage at elevated relative humidity.

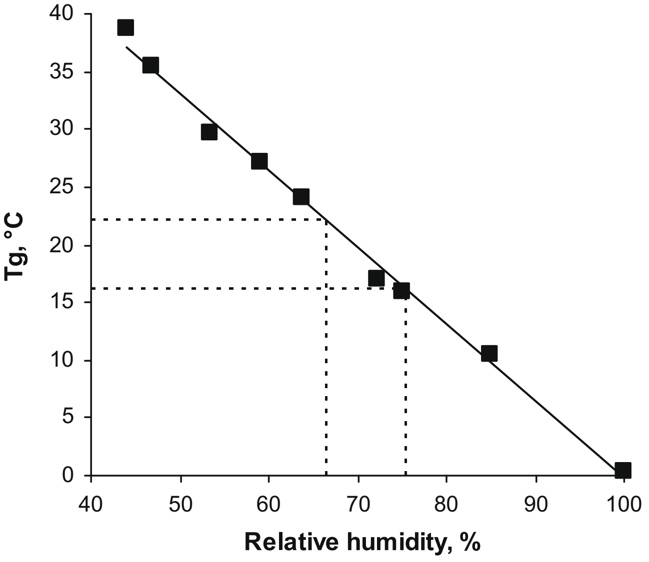

Fig. 7. Dependence of the glass transition temperature (Tg) of Opadry® AMB powder (equilibrated at different relative humidities prior to the DSC measurements) on the RH. The symbols represent the experimentally determined glass transition temperatures, the solid straight line a fitted linear equation (Eq. (7)). The dotted lines indicate the conditions for glassy-to-rubbery state transitions of Opadry® AMB, which were hypothesized based on the observed water uptake kinetics of coated tablets.

Both, PVP and PVPVA increased the glass transition temperature of Opadry® AMB-based films linearly with increasing concentration (Fig. 8). PVP was a more efficient anti-plasticizer for Opadry® AMB than PVPVA (higher increase in Tg) and was, thus, selected for coating trials. In Fig. 9, the experimentally measured water uptake kinetics of tablets containing 100 mg garlic powder coated with Opadry® AMB and 0, 10 and 30% PVP open upon storage at room temperature and 75% RH are shown. Interestingly, and despite what had been expected based on the observed glass transition temperatures of Opadry® AMB/PVP blends (Fig. 8), the water uptake rate increased with increasing PVP amount. This can be attributed to the relatively high hydrophilicity and water permeability of this polymer. The effect of the decrease in the glass transition temperature of the polymeric coating, resulting in decreased macromolecular mobility and, thus, decreased water molecule mobility is overcompensated by the increase in hydrophilicity and permeability of the polymeric network. As expected, the water uptake of the tablets coated with Opadry® AMB/PVP blends decreased with increasing coating level (Fig. 10A, due to the increase in the diffusion pathway length) and increasing curing time (Fig. 10B, due to improved film formation). However, the moisture-protective ability of pure Opadry® AMB-based film coatings was not reached. Thus, the addition of the anti-plasticizing agent PVP to Opadry® AMB was not suitable to improve the performance of this polymeric coating.

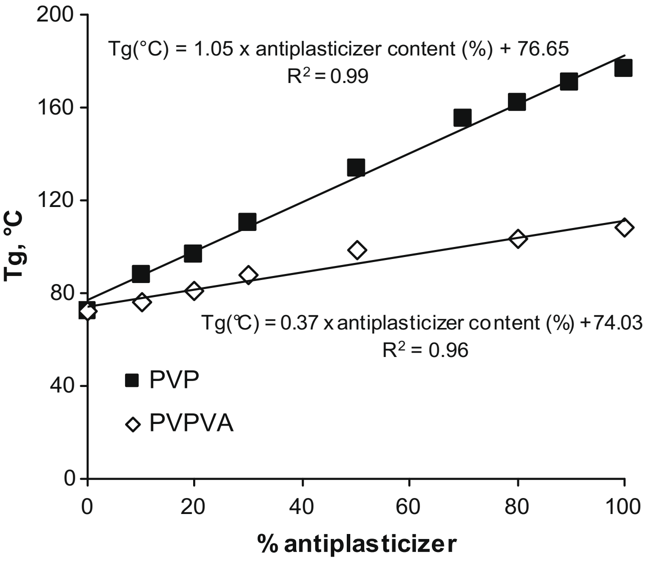

Fig. 8. Glass transition temperature (Tg) of polymeric films consisting of blends of Opadry® AMB and different amounts of poly(vinylpyrrolidone) (PVP) and poly(vinylpyrrolidone)vinylacetate (PVPVA) (acting as anti-plasticizers). The symbols represent the experimentally determined glass transition temperatures, the solid straight lines fitted linear equations (indicated in the figure).

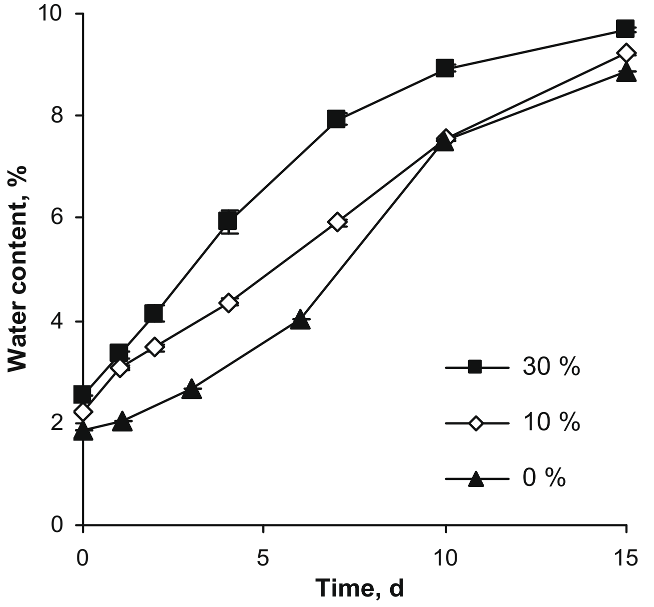

Fig. 9. Water uptake kinetics of tablets containing 100 mg garlic powder coated with Opadry® AMB blended with different amounts of the anti-plasticizer PVP (indicated in the figure) during open storage at room temperature and 75% RH.

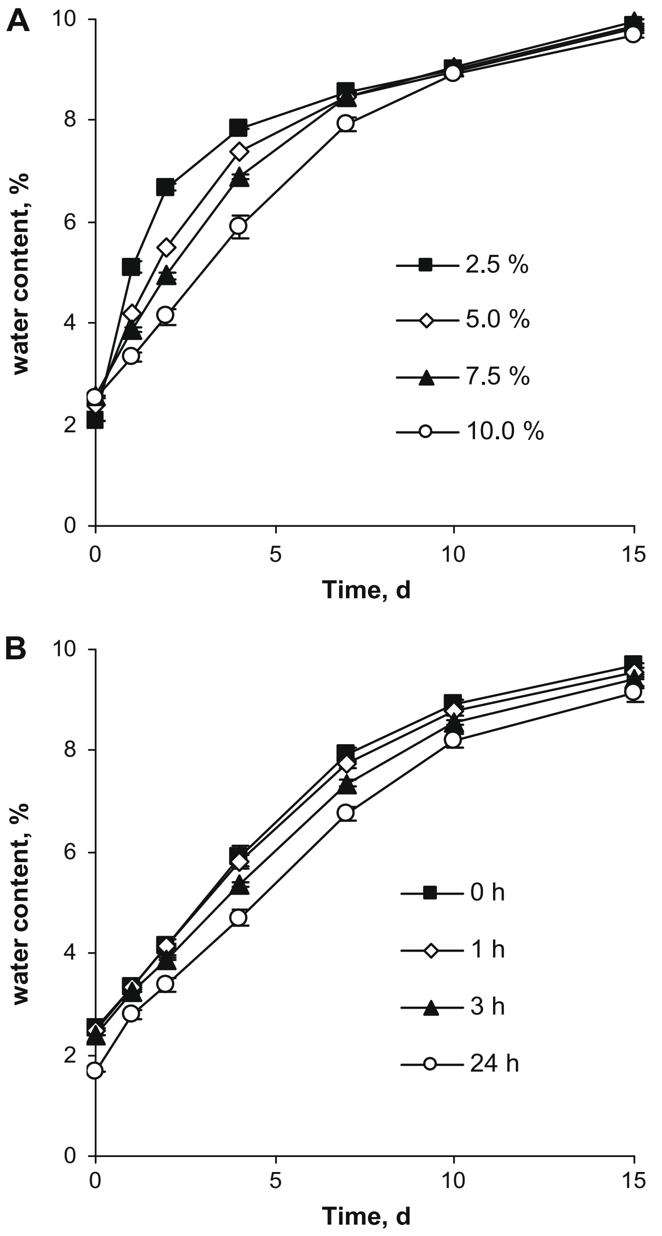

Fig. 10. Water uptake kinetics of tablets containing 100 mg garlic powder coated with Opadry® AMB/PVP 70:30 blends during open storage at room temperature and 75% RH: effects of (A) the coating level (indicated in the figure) and (B) the curing time (indicated in the figure).

4. Conclusions

The present study demonstrates the fundamental importance of the physical state of the macromolecules in polymeric coatings used for moisture protection. Significant structural changes were observed in Opadry® AMB film coatings during storage, whereas Eudragit® E PO barriers remained unchanged during the observation period. The water vapor permeability of Opadry® AMB films strongly depended on the water contents of the systems. The moisture uptake rate of coated tablets fundamentally increased with increasing relative humidity and storage temperature. This could be explained by glassy-to-rubbery state transitions in the polymeric system. Interestingly, linear relationships could be established between the initial water uptake rates and the relative storage humidity or temperature. Below the critical threshold values "66% RH (at room temperature)" and "16 °C (at 75% RH)", water penetration into the dosage forms is significantly reduced.

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