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*Research Article*

*Theme: Advances in Pharmaceutical Excipients Research and Use: Novel Materials, Functionalities and Testing*
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# Investigation into Stability of Poly(Vinyl Alcohol)-Based Opadry® II Films

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***Abstract.*** Poly(vinyl alcohol) (PVA)-based formulations are used for pharmaceutical tablet coating with numerous advantages. Our objective is to study the stability of PVA-based coating films in the presence of acidic additives, alkaline additives, and various common impurities typically found in tablet formulations. Opadry® II 85F was used as the model PVA-based coating formulation. The additives and impurities were incorporated into the polymer suspension prior to film casting. Control and test films were analyzed before and after exposure to 40°C/75% relative humidity. Tests included film disintegration, size-exclusion chromatography, thermal analysis, and microscopy. Under stressed conditions, acidic additives (hydrochloric acid (HCl) and ammonium bisulfate ($NH_4HSO_4$)) negatively impacted Opadry® II 85F film disintegration while NaOH, formaldehyde, and peroxide did not. Absence of PVA species from the disintegration media corresponded to an increase in crystallinity of PVA for reacted films containing HCl. Films with $NH_4HSO_4$ exhibited slower rate of reactivity and less elevation in melting temperature with no clear change in melting enthalpy. Acidic additives posed greater risk of compromise in disintegration of PVA-based coatings than alkaline or common impurities. The mechanism of acid-induced reactivity due to the presence of acidic salts (HCl *vs.* $NH_4HSO_4$) may be different.

**KEY WORDS:** acid salts and stability; pharmaceutical coating; polyethylene glycol; poly(vinyl alcohol).

## INTRODUCTION

In the pharmaceutical industry, there are numerous reasons to film coat tablets. Tablets are film coated to improve appearance and surface finish. Unique colors from the coating can be imparted to tablets for brand identity. Film coatings can also improve swallowing in cases of large tablets or provide taste and/or odor masking. Coated tablets can also be made more resistant to damages such as chipping and erosion due to shipping and handling. In some instances, film coating is applied to act as a moisture barrier to protect moisture-labile tablet formulations.

Poly(vinyl alcohol) (PVA) is a synthetic, hydrophilic polymer that is widely studied for various pharmaceutical applications, including use in controlled release formulations, transdermal delivery systems, and tablet coating. Much research has been conducted on factors that can modify or optimize PVA properties, such as aqueous solubility, swelling, permeability, and drug release rate for these applications. Strategies to modify PVA properties include addition of plasticizers, heat treatment, polymer blends, copolymers, and cross-linking. The versatility and excellent film-forming properties of PVA itself, e.g., biodegradability (1), good strength, and superior appearance, make it a highly suitable polymer for the application of tablet film coating. PVA-based coatings have been found to increase tablet coating efficiency, reduce process time, and enhance tablet-to-tablet uniformity over cellulose-based coatings (5). Additionally, PVA-based coatings also exhibit increased film adhesion compared to cellulose-based coatings (8). Ideally, film coatings should be inert, have minimal interaction with the active species and formulation components, and maintain functionality in the presence of drug molecules (can be acidic or alkaline salts) and common impurities found in excipients. Despite numerous publications on PVA properties, to date, limited work has been done to determine any interaction of PVA-based coatings with components present in the tablet.

The objective of this paper is to study the stability of PVA-based films when acidic and alkaline additives as well as various common impurities typically found in tablet core formulations are incorporated into the film. This simulates

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the intimate contact of these additives/impurities in the tablet core with the coating or in active drug coatings (e.g., acidic drug incorporated into the coating to be coated onto placebo tablets or pellets). Opadry® II 85F is used as a model PVA-based coating formulation in this study. The polymeric components of Opadry® II 85F include PVA and polyethylene glycol (PEG) (2). PEG is the plasticizer in this immediate release coating formulation to enhance film flexibility of PVA (6). PEG has also been found to increase aqueous solubility and swelling of PVA, thus favoring PVA dissolution (6). The outcome of our study is the initial establishment of potential risks, which may cause compromise of film properties on storage under accelerated condition (40°C, 75% relative humidity (RH)) when PVA-based coatings are applied to tablet cores containing these components.

## MATERIALS AND METHODS

### Materials

Opadry® II 85F was provided by Colorcon, Inc (West Point, PA, USA) and used as is. Chemicals (hydrogen peroxide, formaldehyde, hydrochloric acid (HCl), ammonium bisulfate ($NH_4HSO_4$), and sodium hydroxide (NaOH)) were purchased from either EMD Chemicals (Gibbstown, NJ, USA) or J.T. Baker (Phillipsburg, NJ, USA) or Fluka (St Louis, MO, USA). Sodium azide was purchased from Sigma-Aldrich (St. Louis, MO, USA).

## METHODS

### Preparation and Storage of Opadry® II 85F Films

Suspensions of Opadry® II 85F in deionized water (15% *w*/*w*) were prepared by adding the Opadry® powder to water on agitation using a vortex mixer. The suspensions were stirred for at least 1 h before casting into polystyrene dishes and subsequently dried at room temperature and humidity (typically 20–25°C and 20–60% RH) for at least 48 h before testing. Control films were used as is. Acidic additives (HCl, $NH_4HSO_4$), alkaline additive (NaOH), hydrogen peroxide, and formaldehyde were incorporated into the Opadry® II 85F suspension before casting to obtain the test films. HCl and $NH_4HSO_4$ were incorporated to Opadry® II 85F by addition to the polymer suspension to a pH of 2 before film casting. Other additives were incorporated at 1–2% (*w*/*w*) of the total film weight.

Control and test films were analyzed before and after exposure to controlled 40°C/75% RH open for pre-determined time intervals. In some test groups, at least two or more batches of films were made as replicates.

### Film Disintegration

Approximately 25 mg of accurately weighed film was placed in 10 mL water. Within the variation obtained for film thickness and time allowed for disintegration, there was no significant effect of film thickness on disintegration. Therefore, amount of Opadry® film was controlled since it was more significant to influence the percent transmittance at 550 nm. After at least 15 min of continuous stirring with a microstir bar, the extent of film disintegration was measured by turbidity in water. The turbidity was quantified by percent transmittance at 550 nm using a UV/Vis spectrometer (UV-2101 PC, Shimadzu, Columbia, MD, USA).

### Size-Exclusion Chromatography

Following the film disintegration studies, size-exclusion chromatography (SEC) was conducted to characterize dissolved species of PVA and PEG in the disintegration medium before and after accelerated storage condition. To this end, the supernatant liquids from the film disintegration study were loaded into syringes and filtered through 0.45 μm Acrodisc PTFE syringe filters (PALL Life Sciences, East Hills, NY, USA) to prepare samples for SEC analysis. SEC analysis was performed using a Waters 2695 HPLC system equipped with a Waters 2414 refractive index (RI) detector and controlled by Empower chromatography software (Waters Corporation, Milford, MA, USA). The column compartment and detector temperatures were set to 30°C and both the column and detector were equilibrated with 0.1% (*w*/*v*) sodium azide mobile phase prior to use. Separation was performed at 0.5 mL/min using a Shodex 806-MHQ OHpak column equipped with a Shodex OHpak SB-G guard column (Showa Denko, New York, NY, USA). The differential RI signal was collected in positive polarity mode, and the column was calibrated over the molecular weight range of 102–1,200,000 using EasiVail PEG/poly(ethylene oxide) (PEO) standards (Polymer Laboratories, Amherst, MA, USA) constituted in 50 mM citrate, pH 2.8 containing 0.1% (*w*/*v*) LiBr.

### Thermal Analysis

To prepare film samples for analysis by differential scanning calorimetry (DSC), small specimens (<3 mm square) of films were cut and placed in the bottom of standard hermetic aluminum pans (TA Instruments, Wilmington, DE, USA), which were then sealed. Polymer reference samples of PVA and PEG were also prepared in hermetically sealed pans. For both sample types (i.e., films or polymer standards), a total of 4–6 mg was used for DSC analysis. Sealed pans were placed in a TA Instruments (Wilmington, DE, USA) Model 2010 differential scanning calorimeter coupled to a temperature controller and analyzed against a corresponding sealed reference pan; DSC traces were collected between 25 and 350°C at a ramp rate of 10°C/min. The melting temperature ($T_m$) and melting enthalpy of PVA ($\Delta H_f$) were determined for each of the samples using the software (Universal V4.3A TA Instruments). Measurements were conducted in triplicate.

Thermogravimetric analysis (TGA) was used to enable assignment of thermal transitions observed by DSC. Samples (ca. 10 mg) were placed in aluminum TGA pans and heated to 350°C at rate of 10°C/min using a TGA instrument (TGA Q500, TA Instruments, Inc., Wilmington, DE, USA) coupled to a TA controller. Samples were placed in standard hermetic

aluminum pans (TA Instruments) and heated at a ramp rate of 10°C/min up to 350°C with nitrogen as the purging gas.

### Microscopy

Control and test films were observed by optical microscopy (Keyence VHX 600ESO camera, Woodcliff Lake, NJ, USA) and using the VHX-600+500F communication software (Keyence Corporation of America, Woodcliff Lake, NJ, USA) at ×50 magnification.

## RESULTS

### Film Disintegration

Film disintegration and intensity of turbidity of the disintegration medium were used as a primary indicator of coating functionality to disintegrate rapidly, since the Opadry ® film is meant for immediate release. Upon the disintegration of control or unreacted PVA-based coating films in water (disintegration medium) to form a suspension, turbidity was

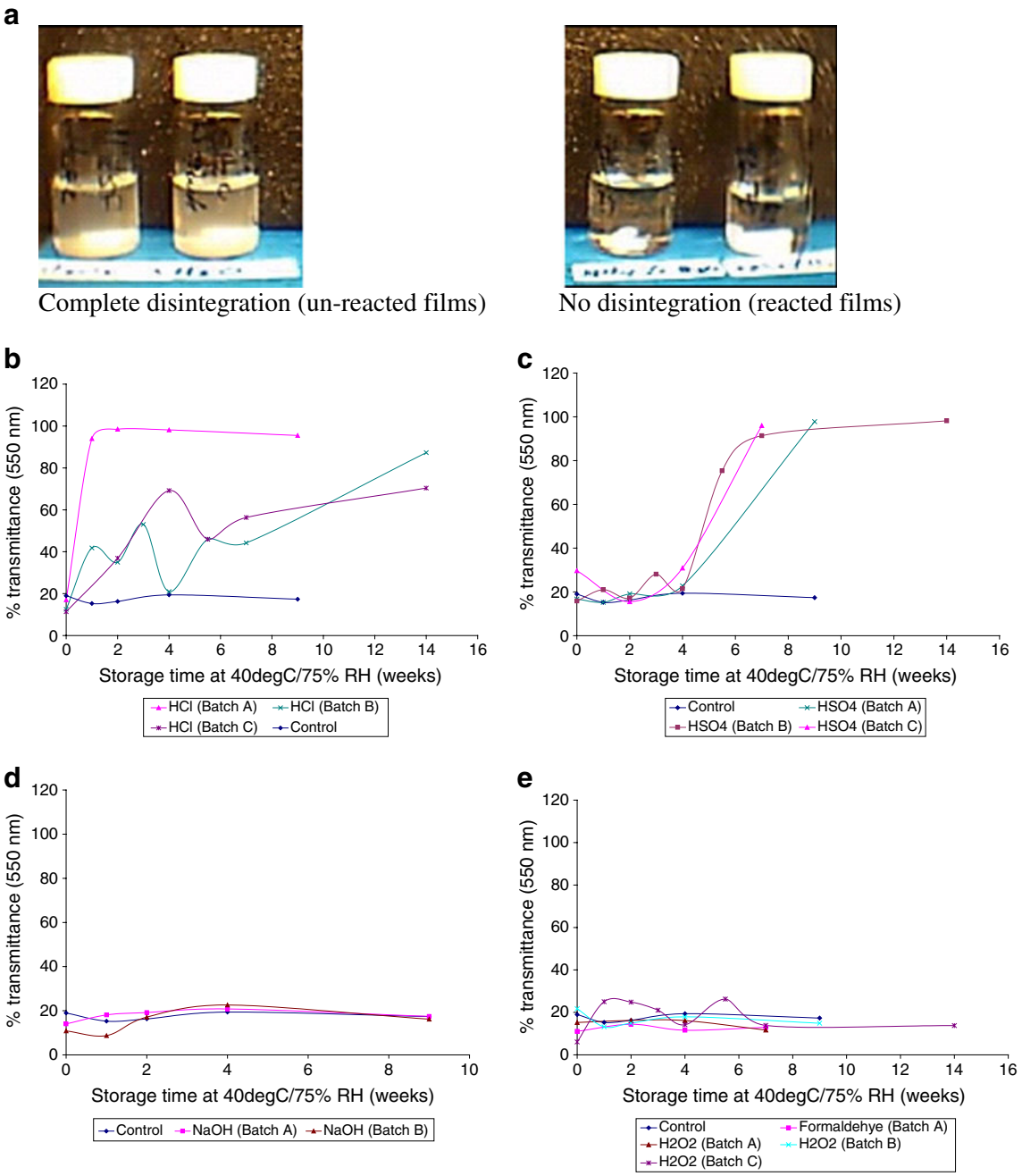



**Fig. 1.** **a** Illustration of complete disintegration of unreacted films and no disintegration of reacted films in the disintegration medium. Percent transmittance of disintegrated samples from films spiked with **b** HCl, **c** $NH_4SO_4$, **d** NaOH, **e** formaldehyde and peroxide compared to control films with increasing storage time at 40°C/75% RH ($N$=1)

observed (Fig. 1a). This indicated that the films were performing according to the requirement of rapid disintegration in aqueous media as immediate release coatings. On the other hand, PVA-based coating films, when reacted with the additives on stressed conditions, would disintegrate to a lesser extent and resulting in lower turbidity (Fig. 1a). The turbidity of the disintegration medium was quantified by percent transmittance at 550 nm. Complete disintegration of films is indicated by low percent transmittance of around 20%, whereas non-disintegrated films would exhibit percent transmittance values approaching 100%. Control Opadry® II 85F films stored under accelerated conditions exhibited complete disintegration up to 9 weeks (Fig. 1b). Disintegration of Opadry® II 85F films spiked with HCl was compromised after storage at 40°C/75% RH. Variability in the relative extent of disintegration was observed for films containing HCl (Fig. 1b). Three batches of films with incorporated HCl were studied and one of the three (batch A) showed complete lack of disintegration after 2 weeks at 40°C/75% RH (Fig. 1b). On the other hand, different batches of films with $NH_4HSO_4$ (Fig. 1c) were less variable. All batches of films containing $NH_4HSO_4$ exhibited little reactivity prior to 4 weeks storage at 40°C/75% RH and compromise of disintegration after 4 weeks.

**Fig. 3.** **a** Size-exclusion chromatographs of **a** 0.1%(*w*/*v*) sodium azide; **b** control film, initial; **c** film with incorporated HCl, initial; **d** control film at 4 weeks 40°C/75% RH; **e** reacted film with HCl at 4 weeks 40°C/75% RH

Films with acidic additives eventually showed complete lack of disintegration (i.e., no turbidity and nearly 100% transmittance) when stored at 40°C/75% RH. Generally, films with incorporated HCl were more reactive than films with incorporated $NH_4HSO_4$ (Fig. 1b *vs*. Fig. 1c). Unlike the instability exhibited by films with acidic additives, films with the alkaline additive, NaOH did not show any compromise in film disintegration (Fig. 1d) up to 9 weeks. Similarly, films with formaldehyde and hydrogen peroxide did not show any compromise in film disintegration (Fig. 1e). Therefore, subsequent investigation focused on reacted films containing acidic additives, with some comparison to NaOH and peroxide-incorporated films.

## Size-Exclusion Chromatography

Figure 2a shows the chromatographs of PVA (18 kDa) and PEG (3.3 kDa) references and that the PVA (18 kDa) and PEG (3.3 kDa) peaks from the

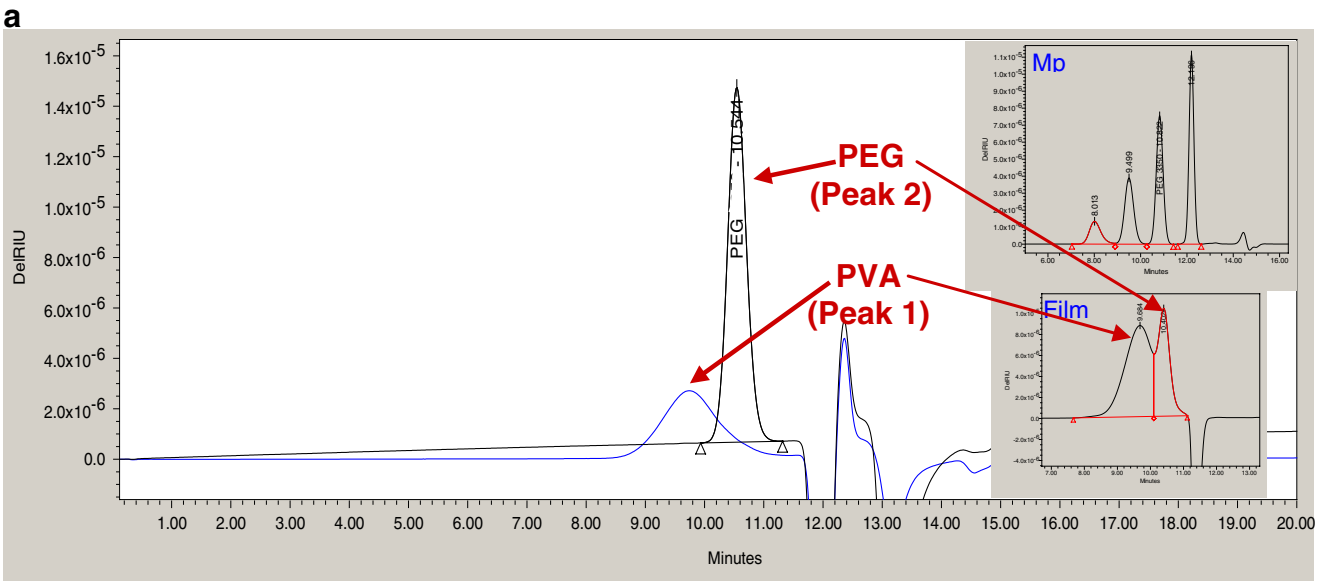
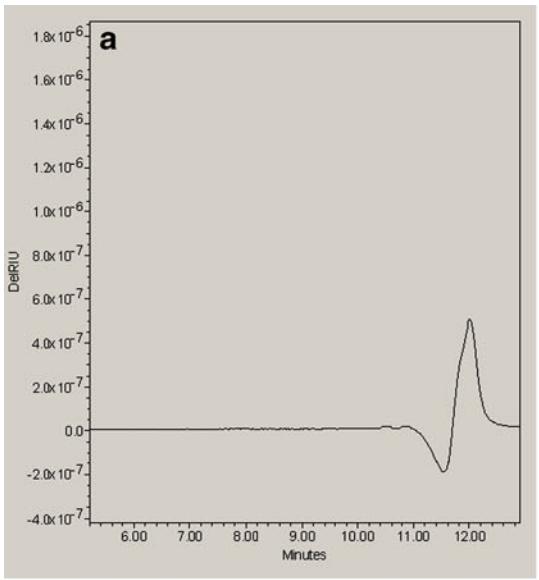



**Fig. 2.** **a** Size-exclusion chromatographs PVA (18 kDa) and PEG (3.3 kDa) references, *insets* are chromatographs of PEO standards (*top*); and Opadry® II 85F film (*bottom*). **b** Calibration plot of log Mp (known peak molecular weight) for PEO standards *versus* retention time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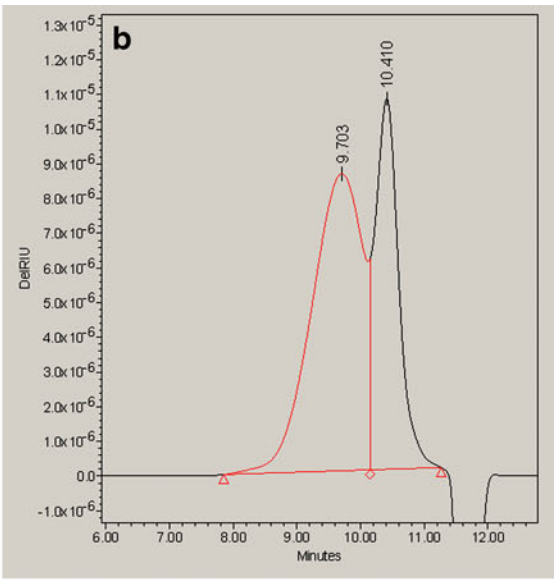
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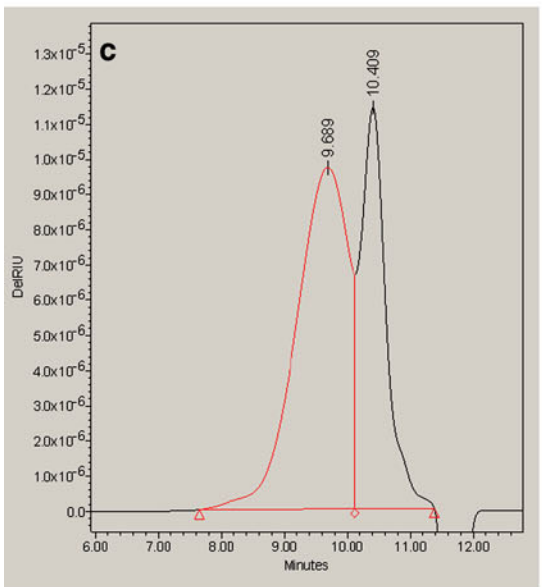
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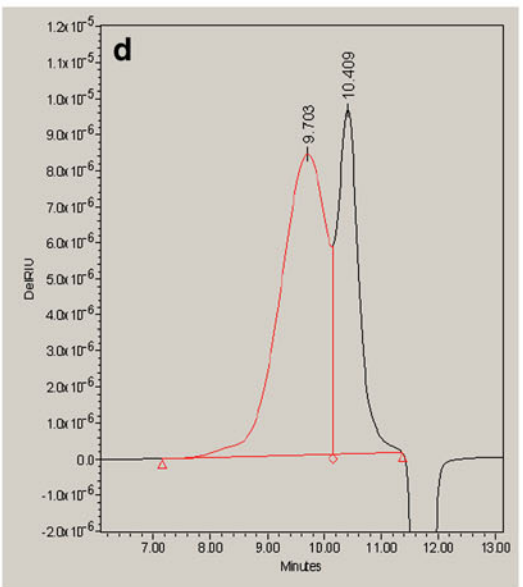
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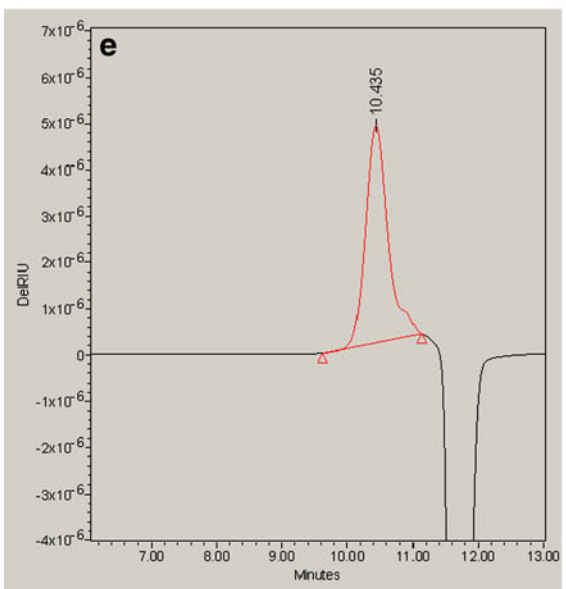
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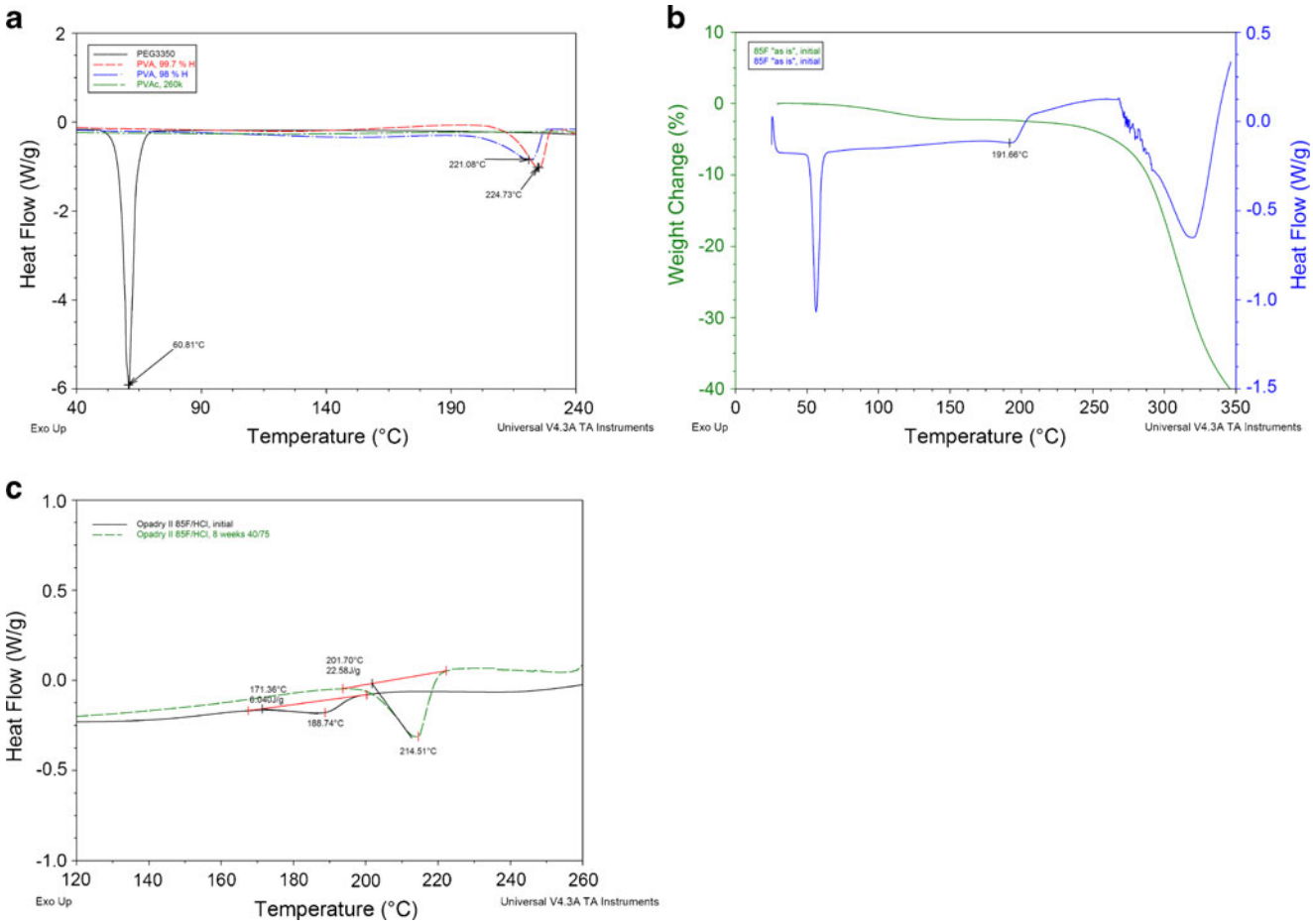


**Fig. 4.** **a** DSC scans of partially hydrolyzed PVA, PVAc and PEG; **b** DSC and TGA scans of control Opadry®II 85F film at initial; **c** melting endotherms of HCl-spiked Opadry®II 85F films at initial and after 8 weeks at 40°C/75% RH

Opadry® II 85F film samples were satisfactorily resolved by SEC. Figure 2b is the calibration plot of log Mp (known peak molecular weight) for PEO standards *versus* retention time. Under the SEC conditions used for this study, there was excellent correlation between log Mp and retention time ($R^2$=0.9997). The turbid disintegration samples were filtered prior to determination of dissolved polymer species in the medium by SEC. Figure 3a shows the size-exclusion chromatograph of the medium alone without test samples. At initial time points, the PVA (18 kDa) and PEG (3.3 kDa) dissolved species can be detected from the control Opadry® II 85F film samples after disintegration, as well as from films with HCl incorporated (Fig. 3b and c). There was no significant difference in the SEC chromatographs of control films and films with HCl incorporated for initial time point films. However, after 4 weeks at 40°C/75% RH, reacted films with HCl evidenced reduced levels of the 18 kDa species (PVA) in the disintegration media relative to the 3.5 kDa species (PEG). These results suggest that lack of disintegration of the reacted film correlates with reduced dissolution of PVA. After 4 weeks, the intensity of the differential RI units was decreased in films containing HCl (Fig. 3d) relative to that of control films (Fig. 3e). This observation was most apparent for reacted films with HCl and did not occur to the same extent for films spiked with $NH_4HSO_4$, NaOH, formaldehyde, and peroxide (data not shown).

## Thermal Analysis

Figure 4a shows the DSC scans of partially hydrolyzed PVA, poly(vinyl acetate) (PVAc), and PEG. Partially hydrolyzed PVA (98%) exhibited a $T_m$ around 221°C, whereas PVA with a higher degree of hydrolysis of 99.7% showed a $T_m$ around 225°C and a slightly higher melting enthalpy ($\Delta H_f$). This melting was not observed for PVAc, the starting material for PVA. The DSC scan of PEG3350 showed an endothermic peak at about 60°C, which is consistent with the melting point of PEG. The DSC and TGA scans of Opadry® II 85F are shown in Fig. 4b. The DSC scan of Opadry® II 85F clearly showed the melting of PEG (endothermic transition at ca. 58–60°C) and the $T_m$ of PVA at 191.66°C with $\Delta H_f$ of ~11 J/g. TGA showed the first weight loss around 100–150°C, which corresponded to moisture vaporization from the Opadry® II 85F film. This weight loss was ranged approximately 2–5%, and there was no trend or significant difference in the moisture loss among the initial and reacted films. The second weight loss corresponded to decomposition, which occurred at temperatures above 250°C.

The PVA melting endotherm was monitored for control and test films before and after storage at 40°C/75% RH. Figure 4c shows the typical PVA melting endotherms of Opadry® II 85F films spiked with HCl at initial and after 8 weeks at 40°C/75% RH. The initial, unstressed Opadry® II

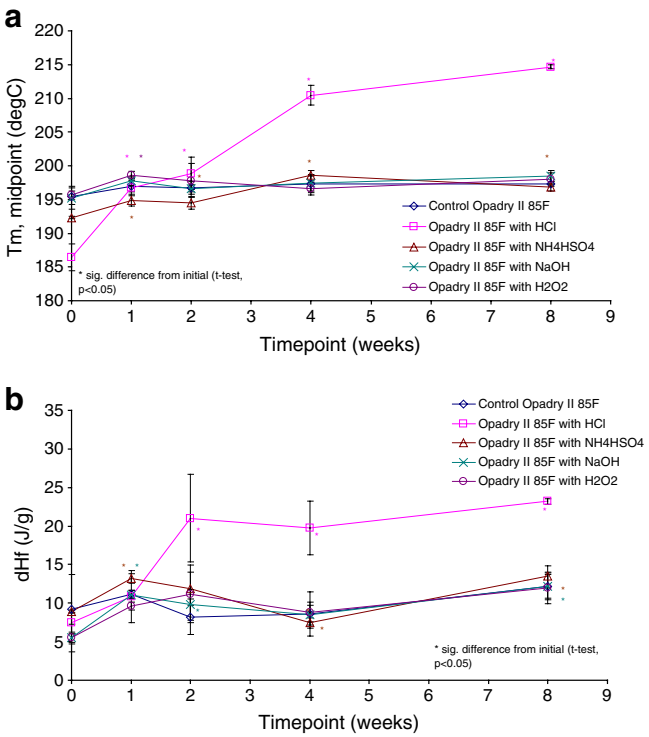


**Fig. 5.** **a** $T_m$, midpoint and **b** heats of PVA melting ($\Delta H_f$) of control films and films spiked with acidic or alkaline additives with storage time at 40°C/75% RH ($N$=3)

85F film with spiked HCl showed a $T_m$ about 188°C ($\Delta H_f$~6–8 J/g). This PVA melting endotherm was shifted to a higher temperature about 214°C and higher $\Delta H_f$ ca. 23 J/g after 8 weeks at 40°C/75% RH. This shift suggests greater thermal stability, potentially due to a change in molecular structure of the reacted film after storage under accelerated conditions. Figure 5a and b show the $T_m$, midpoint, and heats of PVA melting of control films and films spiked with acidic or alkaline additives with storage time at 40°C/75% RH. There was no change in $T_m$ and $\Delta H_f$ for control Opadry® II 85F films and films spiked with $H_2O_2$. On the other hand, there were consistent significant increases in $T_m$ and $\Delta H_f$ from initial for films with HCl incorporated after 1–2 weeks storage at 40°C/75% RH (Figs. 4c and 5). Similarly, there was a significant increase in $T_m$ from initial for films with $NH_4HSO_4$ after 1 week at 40°C/75% RH. However, elevations in $T_m$ for films with $NH_4HSO_4$ incorporated (increase of about 4.5°C after 8 weeks) were less than films with HCl incorporated (increase of about 28.2°C after 8 weeks). Also, there was no clear increasing or decreasing trend for $\Delta H_f$ in films with spiked $NH_4HSO_4$ *versus* the significant increase in $\Delta H_f$ observed in films with spiked HCl. There was no significant change in $T_m$ for films with NaOH incorporated *versus* initial, although $\Delta H_f$ increased significantly from 5.5 (initial) to 12.2 J/g (after 8 weeks storage at 40°C/75% RH).

## Microscopy

Figure 6 shows the appearance of control Opadry® II 85F film and test films spiked with HCl, $NH_4HSO_4$, and NaOH after 18 months at 40°C/75% RH. Discoloration was observed for films spiked with HCl and $NH_4HSO_4$ albeit to different extents. The films containing HCl were slight yellowish whereas the films containing $NH_4HSO_4$ were dark brownish. On the other hand, there was no observable change in appearance from initial for control Opadry® II 85F film and film with NaOH incorporated.

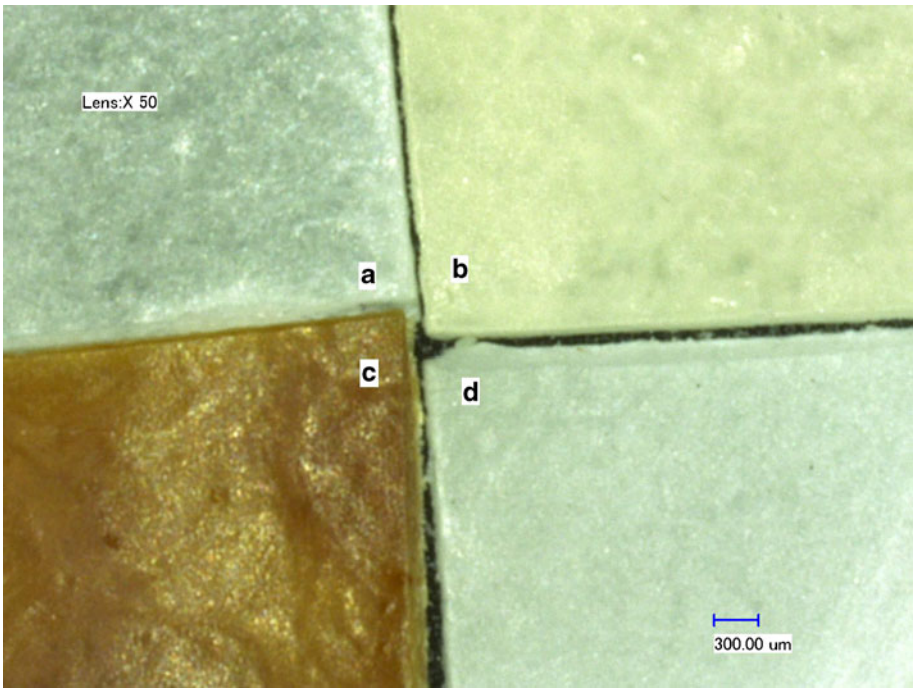


**Fig. 6.** Appearance of **a** control Opadry®II 85F film; and test films spiked with **b** HCl; **c** $NH_4HSO_4$ and **d** NaOH after 18 months at 40°C/75% RH

## DISCUSSION

PVA is a synthetic, non-ionic hydrophilic polymer that is commonly used in aqueous-based film coating for tablets. Rapid disintegration and dissolution is a critical functionality for the Opadry® II 85F film as an immediate-release coating. Research in biodegradation and wastes processes indicates that PVA degradation increases under extremes in pH (10). For thermoplastic processing of PVA, stabilization of PVA blends is obtained by adjusting the pH of the solution between 5.5 and 7.0 before casting the PVA film (1). Here, we found that under stressed storage conditions, acidic additives (HCl and $NH_4HSO_4$) incorporated to the Opadry® II 85F films negatively impacted disintegration, while NaOH did not. The acidic additives were incorporated into the film by adding either HCl or $NH_4HSO_4$ to the polymer suspensions to a pH of 2 before film casting. On the other hand, addition of NaOH to the polymer suspension did not increase pH. Polymer suspensions containing NaOH remained at pH 7 when cast into films. This buffering and neutralization of the effect of added NaOH could be attributed to PVA forming an acidic solution when dissolved in water (9). Thus, alkaline additives posed a lower risk of compromise in disintegration of stressed Opadry® II 85F films than acidic additives. We also observed that films with HCl reacted more quickly albeit with more variability in reaction rate than films with $NH_4HSO_4$. Iordanskii *et al.* studied the diffusion of aqueous acid solutions across PVA films saturated with water, and found that diffusion coefficients of the acids in PVA were closely similar to the values in water (4). The diffusion coefficients of the acids in the PVA matrix were dependent on hydrogen ion concentration and dissociation constants of the acids. Thus, in our study, it is possible that strongly dissociating HCl diffused more rapidly in the polymer matrix and interacted more with PVA than $NH_4HSO_4$ to compromise the disintegration and dissolution of PVA.

Our data suggested that the acid-induced reactivity of Opadry® II 85F films occurred differently using different acid salts (HCl *vs.* $NH_4HSO_4$) to spike the films, besides the rate difference discussed above. Researchers have acknowledged that mechanism of acidic catalysis of PVA degradation in practical use is difficult to define (1). Partly, much research on PVA stability to date has been conducted on pure PVA containing less than 1 mol% acetate groups (3). Here, we observed absence of dissolved PVA species from stressed films spiked with HCl, and a significant increase in $T_m$ and $\Delta H_f$ of PVA. This indicated that increased crystallinity may contribute to hindered dissolution and film disintegration. Films with $NH_4HSO_4$ exhibited less elevation in $T_m$ and no clear change in $\Delta H_f$ of PVA with increasing duration under stressed conditions. Additionally, a difference in the extent of discoloration for the films with different acid salts was observed upon stressed storage for a prolonged period (Fig. 6). Further studies are required to probe mechanistically the acid-induced reactivity of PVA-based films based on these interesting observations.

The control Opadry® II 85F film was opaque in appearance since the formulation contains silicon dioxide in addition to PVA and PEG. Nevertheless, researchers have also reported that films of blends of PVA/PEG were opaque (6,7). This may be due to some immiscibility of PEG in the PVA crystal lattice, although PEG molecules present in the amorphous regions of PVA may physically obstruct the alignment of PVA molecules to form crystallites, thus lowering the $\Delta H_f$ of PVA (6). We also observed lower $T_m$ and $\Delta H_f$ of PVA as formulated Opadry® II 85F *versus* PVA alone and opaque appearance of formulated Opadry® II 85F. No change of properties of the control Opadry® II 85F films upon stressed conditions indicated sufficient stability of this state of PVA lattice with interspersed PEG.

In our study, films with incorporated formaldehyde and hydrogen peroxide showed a comparatively lower risk of compromise in film disintegration and functionality compared to films with acidic additives. However, further studies may be necessary to determine if these common impurities will play a synergistic role in the acid-induced reactivity of Opadry® II 85F films.

## CONCLUSIONS

In this study, we probed the stability of PVA-based coating films in the presence of acidic and alkaline additives, as well as common impurities found in tablet formulations. Under stressed conditions, acidic additives (HCl and $NH_4HSO_4$) negatively impacted Opadry® II 85F disintegration while NaOH, formaldehyde, and peroxide did not. Differences in reactivity were found for stressed films spiked with HCl and $NH_4HSO_4$. Increases in crystallinity of PVA correspond to reduced dissolution of reacted films containing HCl. Reacted films with $NH_4HSO_4$ exhibited slower rate of reactivity and less elevation in $T_m$ with no clear change in $\Delta H_f$. In conclusion, we found that acidic additives posed a greater risk of compromise in disintegration of PVA-based coatings under stressed storage conditions than alkaline or common impurities. It may be interesting to probe the mechanism of acid-induced reactivity caused by acid salts (HCl *vs.* $NH_4HSO_4$) in future studies.

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