Stability Studies of a PEG-Free, PVA-Based Film Coating System

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Purpose

Polyvinyl alcohol (PVA-based) film coatings have been used successfully on a wide range of drug and nutritional supplement products globally since they were introduced by Colorcon in the 1990s.[1] The success of these coating systems has been due to their ability to provide excellent aesthetic performance as well as superior moisture and oxygen barrier properties. In addition, the Opadry® II PVA-based coatings are high productivity systems with high solids and high spray rates resulting in reduced coating process times. The key to achieving high spray rates with the Opadry II PVA-based coatings is the use of polyethylene glycol (PEG) as a detackifing agent. While the use of PEG in film coatings leads to stable drug products in the great majority of cases, there have been instances where PEG has been found to cause instability issues. It has been reported that PEG can degrade oxidatively to formic acid and formaldehyde, which may react with some APIs.[2,3] In addition, PEG can promote color fading of the film coating through oxidation chemistry or due to its mobility under high temperature and humidity conditions.[4] In order to address these potential issues, PEG-free, PVA-based coatings retaining the benefits of high productivity and superior barrier properties have been developed by Colorcon. The purpose of this work was to investigate the levels of formic acid and formaldehyde in a PEG-free, PVA-based film coating system and color stability of coated tablets following storage at ICH accelerated conditions.

Methods

Materials, Storage and Coating Conditions

Formic acid and formaldehyde levels were determined on white PEG-free and PEG-containing, PVA-based coating formulations. Fully formulated coating powders were stored for 6 months in a standard Colorcon package (polyethylene liner within a cardboard box) at 25°C/60% RH, 30°C/65% RH and 40°C/75% RH.

Color stability was investigated using placebo tablets coated with either a PEG-free or PEG-containing PVA-based coating formulation containing 3% FD&C blue #2 aluminum lake pigment. The coatings were applied as 20% solids dispersions in water to a 3% weight gain in a 15" O'Hara Labcoat I coating pan. The coating process parameters used to prepare the coated tablets are shown in Table 1.

Table 1. Coating Process Parameters

Coating Process Parameter	Value
Spray rate (g/min)	20
Inlet air temperature (°C)	65
Tablet bed temperature (°C)	45
Airflow (m^3/hr) (CFM)	250 147
Atomizing air pressure (bar)	1.5
Pan speed (rpm)	18
Spray gun-to-bed distance (cm)	10
Fan air (bar)	1.5

Coated tablets were then stored in HDPE bottles without lids in a stability chamber at 40°C/75% RH.

Formic Acid and Formaldehyde Determination

To facilitate quantification, trace formic acid and formaldehyde were derivatized into ethyl formate and diethoxymethane by placing a 200 mg sample and 2 mL of a 1% solution of p-toluenesulfonic acid in ethanol into a 20 mL headspace vial and equilibrating at 60°C for one hour.[5,6] Samples were analyzed on an Agilent 6890 Gas Chromatograph equipped with a Restek RTX-20 column (30 m length, 0.32 mm inner diameter; 3.0 micron coating thickness). Helium was the carrier gas, set at a constant flow rate of 4.0 mL/min. The column oven temperature was set at 35°C for 5 minutes and then increased to 200°C at a rate of 40°C/min with a final hold time of 1 minute. Chromatographic responses were then quantified using calibration curves developed for standards. The limit of quantification was determined to be 5 ppm for both formic acid and formaldehyde. If a peak was detected below the 5 ppm level, the value was reported as < 5 ppm. Based on select samples run in triplicate, the relative standard deviation (RSD) for formic acid and formaldehyde determinations was < 5% in both cases.

Color Stability

Color difference versus initial was determined, using a reflectance spectrophotometer (Datacolor, Lawrenceville, USA) for each sample following open dish storage at 40°C/75% RH at 1, 2, 3, 4, 8, 12 and 24 week time points.

Results

Formic Acid and Formaldehyde Determination

Levels of formic acid and formaldehyde in PEG-free and PEG-containing formulations following six months storage at various conditions are shown in Tables 2 and 3, respectively.

Table 2. Formic Acid Concentrations Following 6 Months Storage

Formic Acid 6 Month Data (ppm)		
Storage Condition	PEG-Free	PEG-Containing
25°C/60% RH	16	44
30°C/65% RH	16	62
40°C/75% RH	15	72

Table 3. Formaldehyde Concentrations Following 6 Months Storage

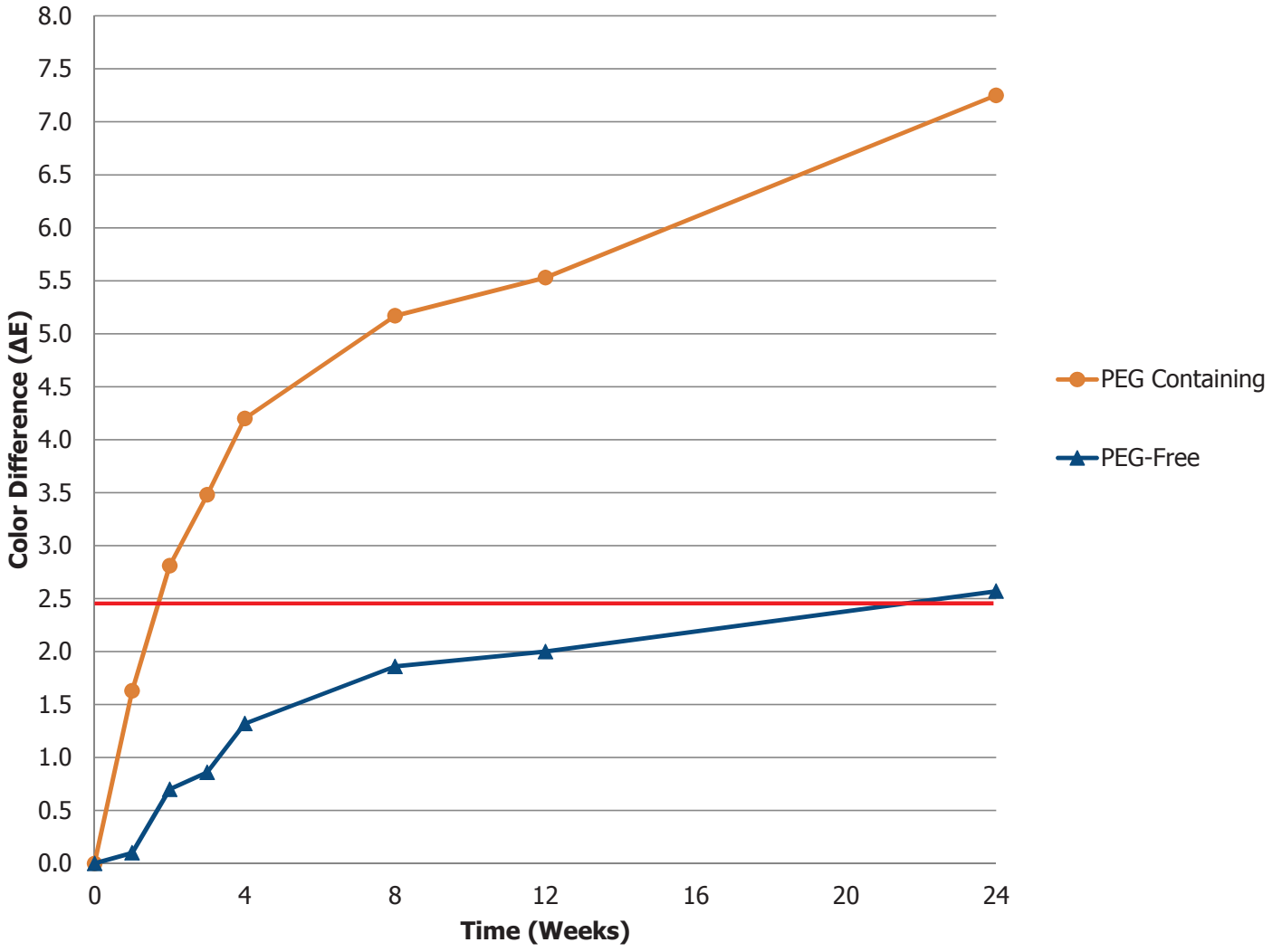
Formaldehyde 6 Month Data (ppm)		
Storage Condition	PEG-Free	PEG-Containing
25°C/60% RH	<5	7
30°C/65% RH	<5	10
40°C/75% RH	<5	7

The formic acid values for the PEG-free coating were significantly lower than those of the PEG-containing formulation and were consistent regardless of storage condition, indicating that formic acid was not formed through 6 months storage stability testing. Formaldehyde levels remained low for both systems.

Color Stability

The color stability of tablets coated with the PEG-free and PEG-containing film coating systems are shown in Figure 1.

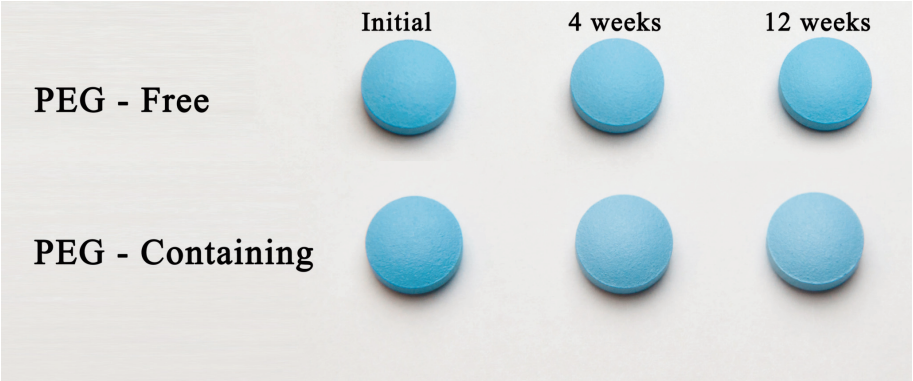
Figure 1. Color Difference of PEG-Free and a PEG-Containing System



After 24 weeks of open dish storage at 40°C/75% RH, the color difference (ΔE) value of the PEG-free formulation was 2.57, while the PEG-containing film coating system was 7.25. The threshold for distinguishing a visible difference for this shade of blue tablet is ΔE = 2.50, as indicated by the red horizontal line in Figure 1.

Images of coated tablets with the PEG-free and PEG-containing formulations following 0, 4 and 12 weeks storage are shown in Figure 2. These images indicate that the PEG-containing tablets are changing color to a lighter shade on storage. There was no visible difference in the color of the PEG-free coated tablets.

Figure 2. Images of Coated Tablets for the PEG-Free and PEG-Containing Formulations at 0, 4 and 12 Week Time Points.



Conclusions

The PEG-free system had minimal levels of formic acid and formaldehyde following 6 months storage. The coated placebo tablets demonstrated excellent open dish color stability following accelerated stability storage conditions. The PEG-free PVA-based system also exhibits high coating productivity and excellent moisture barrier properties, and provides a low risk system for APIs with known sensitivity to PEG and its degradents.

References

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