

Determination of Trace Formic Acid and Formaldehyde in Film Coatings Comprising Polyvinyl Alcohol (PVA)

PURPOSE

Amgen reported the simultaneous determination of formic acid and formaldehyde in pharmaceutical excipients using headspace GC/MS.¹ In the Amgen study, the amounts of formic acid and formaldehyde were determined to be 0-3,080 ppm and 0-86 ppm, respectively, across a range of commonly used excipients; however, PVA was not studied. When attempting to utilize this method for determination of trace amounts of formic acid and formaldehyde in PVA-based film coatings, an interfering peak was encountered. This work will describe the adaptation of the Amgen methodology to determine the amounts of formic acid and formaldehyde in PVA-based film coatings.

METHODS

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. 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 five minutes and then increased to 200°C at a rate of 40°C/min with a final hold time of one 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. If there was no evidence of any peak, the result was reported as not detected (ND). Based on select samples run in triplicate, the relative standard deviation (RSD) for formic acid and formaldehyde determinations was < 5% in both cases.

RESULTS

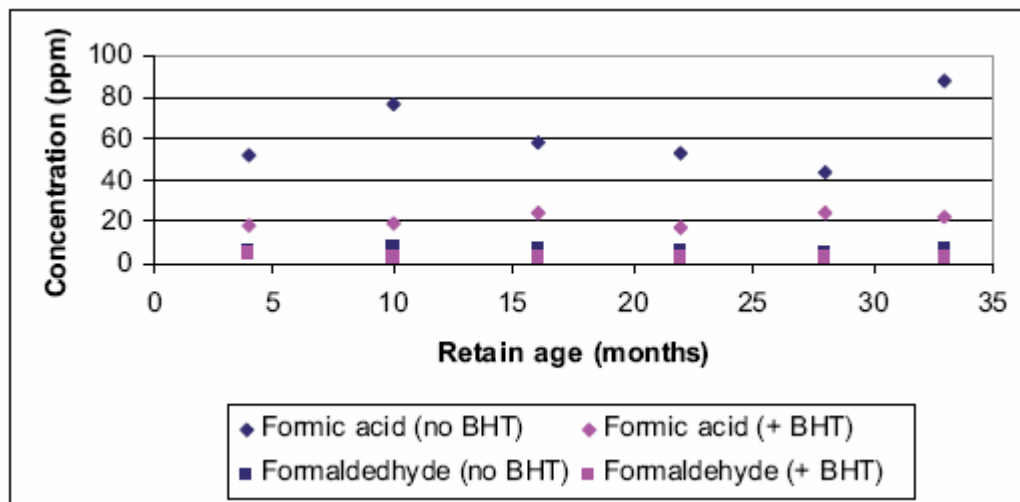
Polyvinyl alcohol contained significantly lower levels of formic acid and formaldehyde than three different low viscosity grades of hypromellose. The formic acid and formaldehyde values determined for hypromellose in this work were consistent with those reported in the Amgen study – formic acid (58.3 and 86.4 ppm) and formaldehyde (11.1 and 15.7 ppm) for the two lots studied. The formic acid concentration in polyethylene glycol was dependent on whether butylated hydroxytoluene (BHT) was present as an antioxidant or not. There was no formic acid or formaldehyde detected in polyethylene glycol 3350 that incorporated BHT; whereas, formic acid and formaldehyde were both detected in polyethylene glycol without BHT. This is consistent with the formation of formaldehyde and formic acid by an autoxidation process.^{2,3} The formic acid concentrations found in the starch-based excipients, Starch 1500 and StarCap 1500, were dramatically lower than those for Povidone, which were reported to be as high as 3,080 ppm in the Amgen study.

Table 1. Formic Acid and Formaldehyde Concentrations for Select Polymers, Plasticizers, and Core Excipients

Raw material description	Number of lots	Average formic acid concentration & (standard deviation) ppm	Average formaldehyde concentration & (standard deviation) ppm
Polyvinyl alcohol	12	34.2 (6.0)	5.6 (2.6)
Hypromellose 2906 (3 cps)	6	57.7 (10.7)	9.0 (0.6)
Hypromellose 2906 (6 cps)	6	97.5 (27.5)	14.7 (3.3)
Hypromellose 2906 (15 cps)	6	67.7 (25.9)	12.8 (5.7)
Polyethylene glycol 400 (no BHT)	3	14.7 (7.6)	7.7 (2.3)
Polyethylene glycol 3350 (no BHT)	3	10.3 (2.1)	< 5
Polyethylene glycol 3350 (w/ BHT)	3	ND	ND
Triacetin	3	16.3 (5.5)	ND
Starch 1500 [®] partially pregelatinized maize starch	3	< 5	ND
StarCap 1500 [®] co-processed starch excipient	6	10.2 (1.3)	ND

Formic acid and formaldehyde were also determined in PVA-based film coatings incorporating PEG 3350. Opadry[®] II, high performance film coating system, (85F18378 white) contained PEG 3350 with BHT; whereas, Opadry II (85F18422 white) contained PEG 3350 without BHT. Six lots of each film coating formulation were analyzed. 85F18378 contained consistently lower levels of formic acid versus 85F18422 (Figure 1). Formaldehyde levels were close to the limit of quantification (5 ppm) for both formula types. Neither formic acid nor formaldehyde concentration was dependent on the age of sealed retains (4-33 months) for either film coating formulation. These retains were stored at ambient temperature of less than 30°C.

Figure 1. Formic Acid & Formaldehyde Concentrations in PVA-Based Film Coatings of Varying Age and with Different Grades of PEG 3350



CONCLUSIONS:

A GC method was successfully adapted to quantify the trace amounts of formic acid and formaldehyde in PVA-based film coatings. Formic acid and formaldehyde were determined to be in the range of 15-90 and 0-9 ppm, respectively, in PVA-based film coatings. Typical formic acid and formaldehyde levels in PVA alone were determined to be 25-50 ppm and about 5 ppm (limit of quantification), respectively. The variation in the levels in the film coating formulations was attributed to the amounts of formic acid and formaldehyde found in different grades of polyethylene glycol 3350 (a component in the fully-formulated PVA-based film coatings). The levels of formic acid and formaldehyde in PVA-based film coating formulations were not dependent on the ages of lots studied.

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