The Effect of Crosslinker Structure Upon the Rate of Hydroperoxide Formation in Dried, Crosslinked Poly(vinylpyrrolidone)

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ABSTRACT: The hydroperoxide levels of two commercial types of crosslinked poly(vinylpolypyrrolidinone) (or crospovidone) disintegrants were studied as a function of time and temperature using the titanyl sulfate titration method. It was noted that the two crospovidone types exhibited significantly different rates of hydroperoxide buildup and that this difference increases with increasing temperature. While the chemical and physical structures of these commercial types are essentially the same, they are known to be different with respect to their crosslinkers which represent nominally 2% of the total mass. These crosslinkers are 3-ethylidene-*N*-vinyl-2-pyrrolidinone and *N*,*N*′-divinylimidazolidinone. While both contain lactam type rings, the latter possesses two nitrogen atoms versus one in the former. It was hypothesized that this difference in the number of heteroatoms results in a greater susceptibility to oxidative attack at carbon positions vicinal to these nitrogen atoms. To test this hypothesis, model compounds representing the two crosslinker ring structures were subjected to oxidative attack and analyzed for hydroperoxide buildup over time and at several temperatures. The results of the model compound study were consistent with the observations made for hydroperoxide buildup in the corresponding crospovidone types thereby supporting this hypothesis. © 2007 Wiley Periodicals, Inc. J Appl Polym Sci 107: 2776–2785, 2008

Key words: ageing; degradation; drug delivery systems; polylactams; solid-state structure

INTRODUCTION

As a result of its highly hydrophilic character and rapid swellability in aqueous media, crosslinked, insoluble poly(vinylpyrrolidinone) (PVP)or poly(vinylpyrrolidone) (or polyvinylpolypyrrolidone or crospovidone USP/EP/JPE) is used extensively as a pharmaceutical tablet disintegrant.[1] There are currently two principal processes used to make crospovidone commercially via free radical proliferous (or popcorn) polymerization. Neither process employs a free radical polymerization initiator. The original process (which will be referred to as Type A) involves the reaction of *N*-vinyl-2-pyrrolidinone monomer at temperatures in excess of 100°C in the presence of an alkali metal hydroxide and a small amount of water.[2] It has been shown that this process generates several crosslinkers in situ as a result of the reaction of the monomer with the alkali metal hydroxide.[3,4] These are primarily 3-ethylidene-*N*-vinyl-2-pyrrolidinone, and to a much lesser extent, ethylidene-bis-3-(*N*-vinyl-2-pyrrolidinone). A subsequent process (which will be referred to as Type B) involves heating an aqueous solution of *N*-vinyl-2-pyrrolidinone to a temperature above 100°C in the presence of a deliberately added, alternate crosslinker, *N*,*N*′-divinylimidazolidone (or *N*,*N*′-divinylethyleneurea).[5] Both processes result in a material which is insoluble in water and only slightly swellable due to the formation of chemical crosslinks and a high degree of polymer chain physical entanglement. Pyrolysis-GC/MS has been employed both to identify and to determine the amount of any of these crosslinkers incorporated into the structures of the final crospovidone products, typically in the range of 1.8–2.5% (w/w).[6]

Peroxide impurities have been reported to develop in the powder form of povidone and crospovidone as a result of air oxidation.[7] The only current monograph requirement for a maximum level of residual peroxide in crospovidone (primarily hydroperoxide calculated as hydrogen peroxide) is found in the European Pharmacopeia (EP).[8] The present limit is set at 400 ppm. The potency of a drug substance formulated with crospovidone possessing high levels of peroxide impurities can be decreased through oxidative degradation. The formulated product's shelf life can also be adversely affected. In 2000, it was reported that raloxifene hydrochloride, a selective estrogen receptor modu-

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lator useful in the treatment of osteoporosis, had been oxidatively degraded when formulated with crospovidone and/or povidone PVP excipients.[9] The authors provided evidence which indicated that an amine oxide degradant, raloxifene *N*-oxide, was formed as a result of peroxide impurities present in these excipients. This finding is consistent with the reaction of peroxides with tertiary amine functionalities, common sites for electron-transfer induced oxidation.[10]

The original purpose of this study was to develop an understanding of the rate of peroxide buildup in crospovidone powder as a function of temperature upon exposure to air. Materials made by both commercial processes, Types A and B, were studied and their rates compared. The marked difference found in the peroxide buildup in the two material types was hypothesized to be due to the chemical structural difference between these disintegrants, namely the crosslinker moieties, comprising $\sim$ 2% of the mass. Analogous, low molecular weight model compounds were selected to represent each of the crosslinker structures and tested for their relative reactivity to oxidative attack. Thus, the additional purpose of this work was to relate the results of this model compound study to the peroxide impurity growth in the two crospovidone types to test this hypothesis.

EXPERIMENTAL

Materials and methods

Most chemicals including 1,3-dimethyl-2-imidazolidinone and 1-methyl-2-pyrrolidinone were reagent grade and purchased from Aldrich Chemicals, Milwaukee, Wisconsin. All Type A crospovidone samples and Source 1 PVP were obtained directly from International Specialty Products, Wayne, NJ. All Type B crospovidone and Source 2 PVP samples were obtained from BASF AG, Ludwigshafen, Germany. Titanium(III) Chloride solution, was obtained from EM Science no. 808307-2, Gibbstown, NJ. It is sold as 15% titanium trichloride in 10% hydrochloric acid. Concentrated sulfuric acid ($\approx$96%), was purchased from JT Baker, Phillipsburg, NJ. All glassware including coarse fritted-glass gas dispersion tubes, (24/40) to 7 mm reducing adapters and stoppers, 2L three-necked (24/40) round-bottom flasks, and (24/40) 2 foot air-cooled Vigreux condensers were purchased from Kimble/Kontes, Vineland, NJ. Precision 12-L digital water baths, Dow Corning silicone vacuum grease (1597418), and 1/4 I.D./5/16 O.D. PTFE tubing were obtained from VWR International, West Chester, PA. Anko's MITY-FLEX 907-282 peristaltic pumps were purchased from McMaster Carr Supply, Los Angeles, CA.

Hydroperoxide determination

The British/European Pharmacopoeia method was used for the determination of hydroperoxide content in the samples studied. In this method, a 2 g sample was suspended in water while the hydroperoxides were reacted with titanium(III) trichloride-sulfuric acid reagent. The suspension was then filtered and the absorbance of the filtrate measured at 405 nm. A minor modification of this method was made which allowed the reagent solution to be prepared freshly in the laboratory. In particular, the titanium(III) chloride-sulfuric acid reagent was prepared in the laboratory by addition of sulfuric acid to a titanium(III) chloride solution (purchased from EM Science) containing about 15% (w/v) of $TiCl_3$ in hydrochloric acid [10% (w/v) HCl]. Method equivalency between the two methods was demonstrated. The pharmacopoeial method is qualitative in nature and states an absorbance limit that correlates to either 400 ppm or 1000 ppm depending upon the particle size of the material. To produce quantitative results, the pharmacopoeial method was enhanced with the addition of peroxide standard solutions of known concentration. These solutions were then reacted with the titanium(III) trichloride-sulfuric acid reagent and their absorbancies measured at 405 nm. A linear calibration was developed and used for quantitative analysis. The working range of this modified method is 12–500 ppm hydroperoxide in the sample.

Peroxide buildup in PVP and crosslinked PVP powders

Crosslinked PVP powders (10 g) were stored in wide-mouth high-density polyethylene containers with screw-on lids with an air headspace. Type A crospovidone samples were obtained immediately after production, while Type B samples were stored in sealed vacuum packed foil bags to ensure freshness until used in this study. Samples were aged in a refrigerator (4°C), ambient lab space (23°C), or in a 40°C/75% relative humidity (RH) chamber. Peroxide content was determined by the titanyl-sulfate method, as outlined above. This method quantifies both H_2O_2 and hydroperoxides (but not hindered peroxides). Similarly, soluble Source 1 and Source 2 PVP powders were aged at 20–25°C and 40°C.

Peroxide buildup in model crosslinker analogs

One liter of each crosslinker analog was added to a (24/40) three-necked round bottom flask. The coarse-fritted gas dispersion tube was placed in the center neck by a (24/40) to 7 mm reducing adapter and sealed by a Viton O-ring. The gas dispersion tube was then attached to the outlet of a peristaltic

pump by a 1/4 I.D./5/16 O.D. PTFE tubing. Likewise, one of the two remaining necks was used to create a recycle loop by attaching a (24/40) two-foot air-cooled Vigreux condenser into one neck of the flask, and connecting one end of the PFTE tubing through the (24/40) to 7 mm reducing adapter to the top of the condensing column while the other end was attached to the inlet of the peristaltic pump. The remaining neck was stoppered and served as a sampling port to remove 10 mL aliquots daily. All ground glass connections were then sealed with stiff high temperature silicone vacuum grease.

Each respective analog flask was then immersed in a 12-L digital water bath. Peroxide buildup in the model crosslinker analogs was achieved by bubbling air through the coarse fritted gas dispersion tube at a rate of 987 mL/min by the peristaltic pump, at temperatures of 25, 45, or 65°C as maintained in each condition by a dedicated water bath. The whole system remained closed by using a recycle loop on the vessel to prevent loss of any volatile components, which in turn, could erroneously raise the peroxide content by evaporation. Aliquots were then removed daily to determine the peroxide level for each analog maintained at the three aforementioned temperature conditions.

FTIR analysis

The sample preparation for this experiment used a 1 wt % polymer solution in water that was cast onto a ZnSe disc and allowed to air-dry prior to IR analysis. A Mattson Galaxy 3020 FTIR was used for this analysis. The infrared spectrum obtained, employed a spectral width of 4000–600 cm^{-1} at 4 cm^{-1} resolution and 16 repetitive scans.

13C-NMR analysis

To spectroscopically characterize the samples ^{13}C FT-NMR was employed. To prepare the samples for the NMR spectroscopic characterization, 0.6 g of polymer was dissolved into 3 mL of DMSO-d6 and placed into a 10 mm NMR tube. To perform the analysis, a Varian Inova 400 MHz NMR spectrometer was utilized and the instrumental parameters for these experiments employed a spectral window of 25,000 Hz defined by 16K number of complex data points, a 1 s relaxation delay, and at least 2048 repetitive scans at room temperature 25°C.

RESULTS AND DISCUSSION

Peroxide buildup in soluble PVP

PVP is produced by solution free radical polymerization. Commercial PVP solutions (which have not been prepared from air-dried powders) contain nondetectable level of peroxides. They will not build up peroxides nor decrease in molecular weight upon storage in the presence of oxygen under ambient temperature. Likewise, PVP freeze-dried (under vacuum) from commercial PVP solutions does not increase in peroxides. This indicates the PVP polymer molecules are inherently stable and are not attacked by oxygen at ambient temperature in the complete absence of initiating radicals.

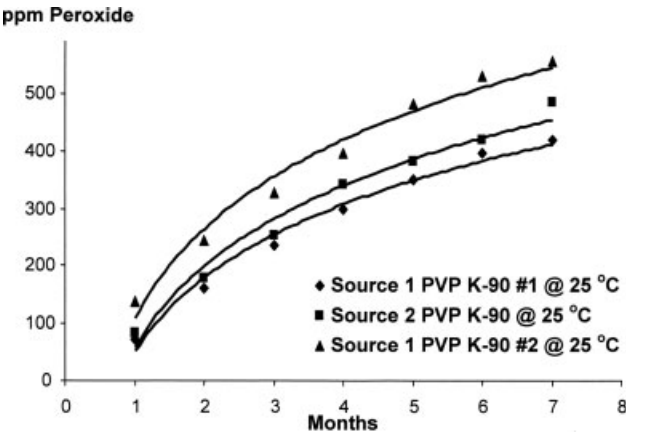

Figure 1 Peroxide buildup in Source 1 and Source 2 PVP K-90 at 25°C.

In contrast, commercial PVP powders which are spray-dried, drum-dried, or belt-dried from PVP solutions will increase in peroxides with time upon storage in the presence of oxygen at ambient temperature. The high temperature (~ 200°C) commercial drum-drying process in the presence of oxygen introduces very low (ppm) levels of hydroperoxide into the PVP powders. The hydroperoxide level will increase in PVP powders upon storage in the presence of oxygen at ambient temperature. Furthermore, the rate of peroxide increase in PVP is accelerated by increasing temperature.

The peroxide buildup for soluble drum-dried PVP K-90 from commercial Source 1 and from commercial Source 2 in an air headspace over a 7-month period is depicted in Figure 1. It is noteworthy that a higher initial level of hydroperoxide will cause even higher levels to be generated over time, but that the rate for peroxide buildup is relatively constant among all the PVP samples examined within this set. Furthermore, the type of drying process used can greatly affect the peroxide buildup rate. In particular, comparison of drum-dried PVP that is also mechanically milled to the requisite particle size versus spray-dried PVP clearly indicates a faster buildup in hydroperoxides for the drum-dried product than the spray-dried material, Figure 2.

It is envisioned that at the higher temperature and longer residence time of the drum-drying process

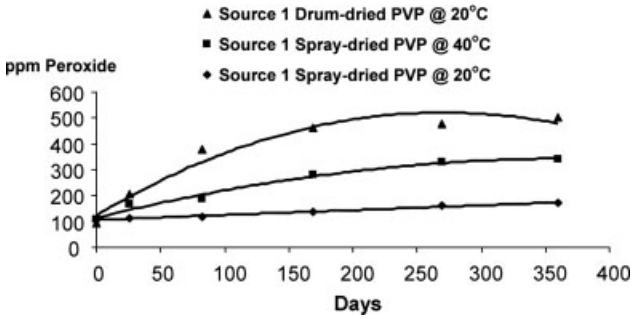

Figure 2 Peroxide buildup in Source 1 Drum-dried PVP at 20 vs. Spray-dried PVP at 20°C and 40°C.

(200+°C), along with the mechanical fractures caused by the milling process introduce more free-radicals on the surface of the material in contrast to the spray-drying process (at 100°C). It is also noteworthy to focus on the temperature dependency of hydroperoxide buildup within similarly dried material. In particular, raising the ageing temperature from 20 to 40°C for the spray-dried PVP, results in a significant increase in the rate of peroxide buildup, as illustrated in Figure 2.

These data indicates that the oxidation reaction of commercial PVP polymers is a chain reaction and is auto-catalytic in the presence of air or oxygen. Traces of free radicals caused by mechanical fracture and heat during processing are responsible for the initiation of this chain reaction. These initiating radicals react with oxygen to form hydroperoxides. The hydroperoxides then act catalytically on the polymer to generate more hydroperoxide over time.

The molecular weight degradation mechanism of high molecular weight polymers due to hydroperoxides has long been known.[11] Decomposition of hydroperoxides on tertiary carbon atoms leads to cleavage of carbon–carbon bonds in the main chain as shown in Figure 3.[12,13] This is the primary mechanism for K-value (M_w) loss with time in high molecular weight (e.g., $M_w = 1.1 \times 10^6$ Da) PVP powder products in the presence of oxygen.

However, oxidation of PVP can also occur on the pyrrolidinone side-chain as depicted in Figure 4. The catalytic auto-oxidation cycle is generated when the initial hydroperoxide (III) decomposes and attacks another pyrrolidinone ring by hydrogen abstraction thereby generating the highly reactive pyrrolidinone radical (IV). This radical in turns reacts with oxygen to generate the peroxide-pyrrolidinone radical (II), which in turns reacts with another pyrrolidinone ring to reactivate the cycle. Ultimately, the oxidation of the pyrrolidinone ring to the succinimide functionality (VI) has been confirmed by FTIR and 13C-NMR analyses in our laboratories.

Direct evidence for succinimide formation by either thermal degradation in air, or by peroxide-mediated oxidation of PVP by sodium hypochlorite, is illustrated in Figures 5 and 6 for PVP and sodium hypochlorite oxidized PVP, respectively. The appearance of two new carbonyl stretching bands at 1767 and 1693 cm^{-1} is clearly consistent with the cyclic-imide functionality, exhibiting its out-of-phase and in-phase stretches, respectively, as shown in Figure 6. Likewise, 13C-NMR results indicate two new signals attributable to the symmetrical alpha-methylene carbons at 28 ppm (labeled as no. 9), and a new carbonyl at 178 ppm (labeled as no. 8) in DMSO at 25°C, Figure 7.

Peroxide buildup in crosslinked PVP

Under the same set of conditions previously outlined, we also evaluated the peroxide buildup in crosslinked PVP's. In particular, crospovidone Type A and B samples were compared. Identical to the soluble PVP results, increasing the temperature resulted in increasing the rate of peroxide buildup for the crosslinked PVP over a 700-day time period. It is noteworthy that at both ambient temperature (23°C) and at 40°C, a plateau on peroxide buildup is observed in the first 6–12 months with a slight decrease after 18 months as seen in Figure 8.

Initially, these findings are consistent with a zero-order reaction whereby there is an initial linear buildup at oxygen sensitive sites to form hydroperoxides. However, this initial rate is tempered by concerted secondary side-reactions that lead to succinimide formation as already described above. This results in slowing the rate in hydroperoxide buildup, and ultimately reducing the overall level in these crospovidone products.

More importantly however, when one compares the initial rates for Type A with Type B crospovidone at any given temperature, the peroxide buildup rate is significantly higher in the Type B crospovi-

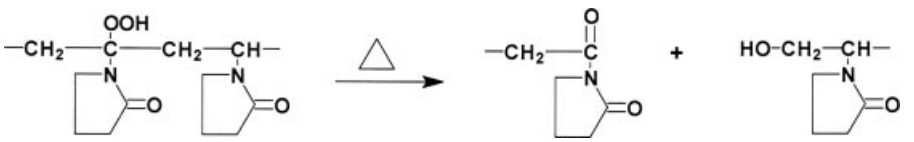

Figure 3 Mechanism of degradation of high MW PVP by hydroperoxidation.

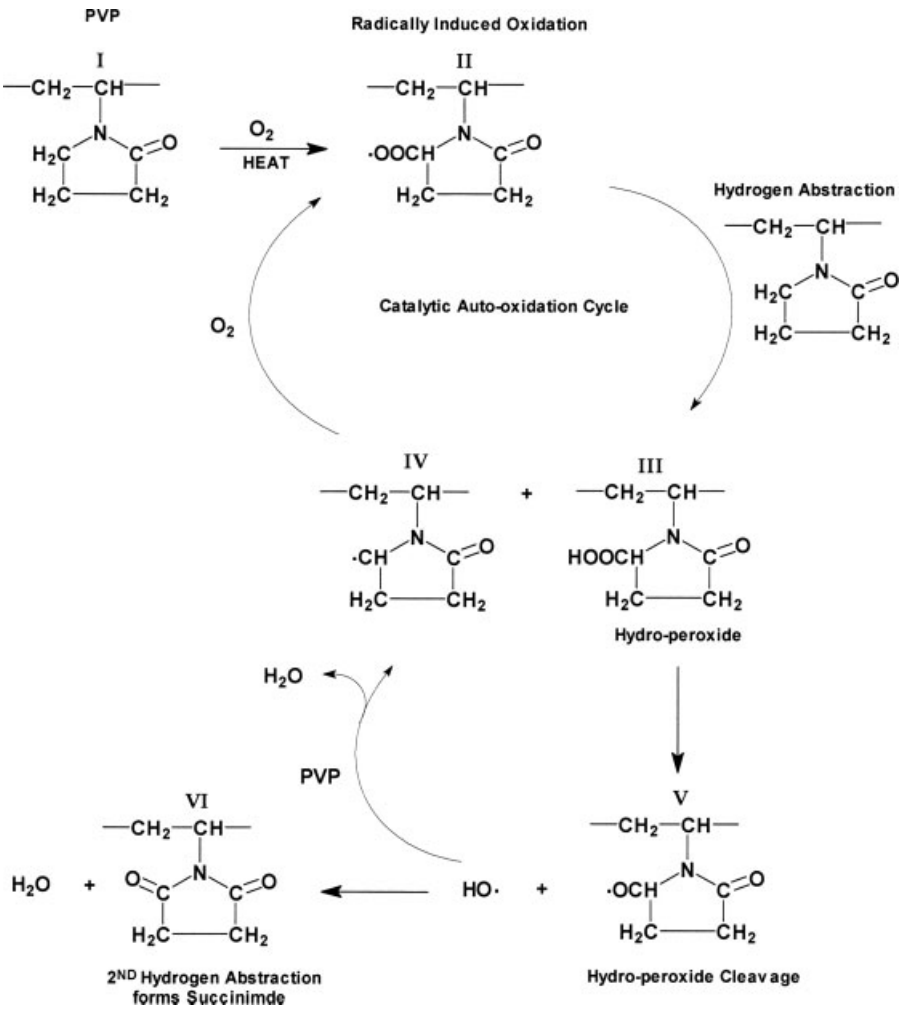

Figure 4 Mechanism of hydroperoxidation of PVP's pendant ring.

done by at least a factor of two when compared to its Type A counterpart at ambient temperature or above (Figure 8 and Tables I and II). These findings would indicate that the Type B crospovidone material has an inherent feature which causes the rate of buildup and level of hydroperoxide reached under identical conditions to be greater than the Type A counterpart. It should also be noted that both products are unmilled and use the same drying process, so that this difference is not related to the type of drying employed, as seen earlier.

As a consequence, Type B crospovidone can have a greater deleterious effect upon pharmaceutical formulations that contain peroxide-sensitive drugs

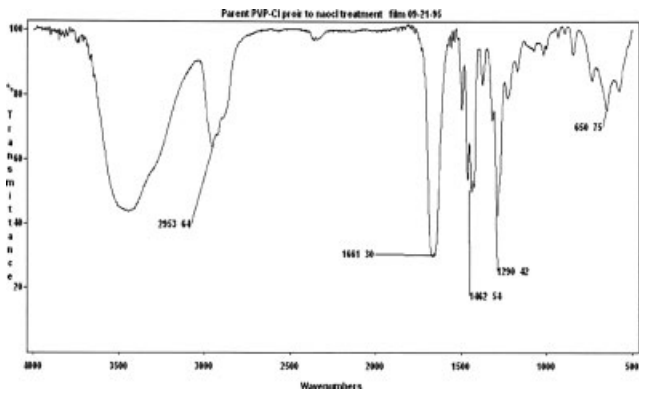

Figure 5 FTIR profile for standard PVP prior to sodium hypochlorite treatment.

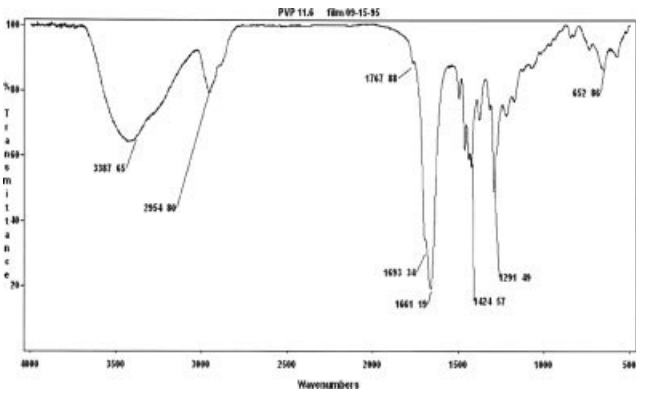

Figure 6 FTIR profile for standard PVP after sodium hypochlorite treatment.

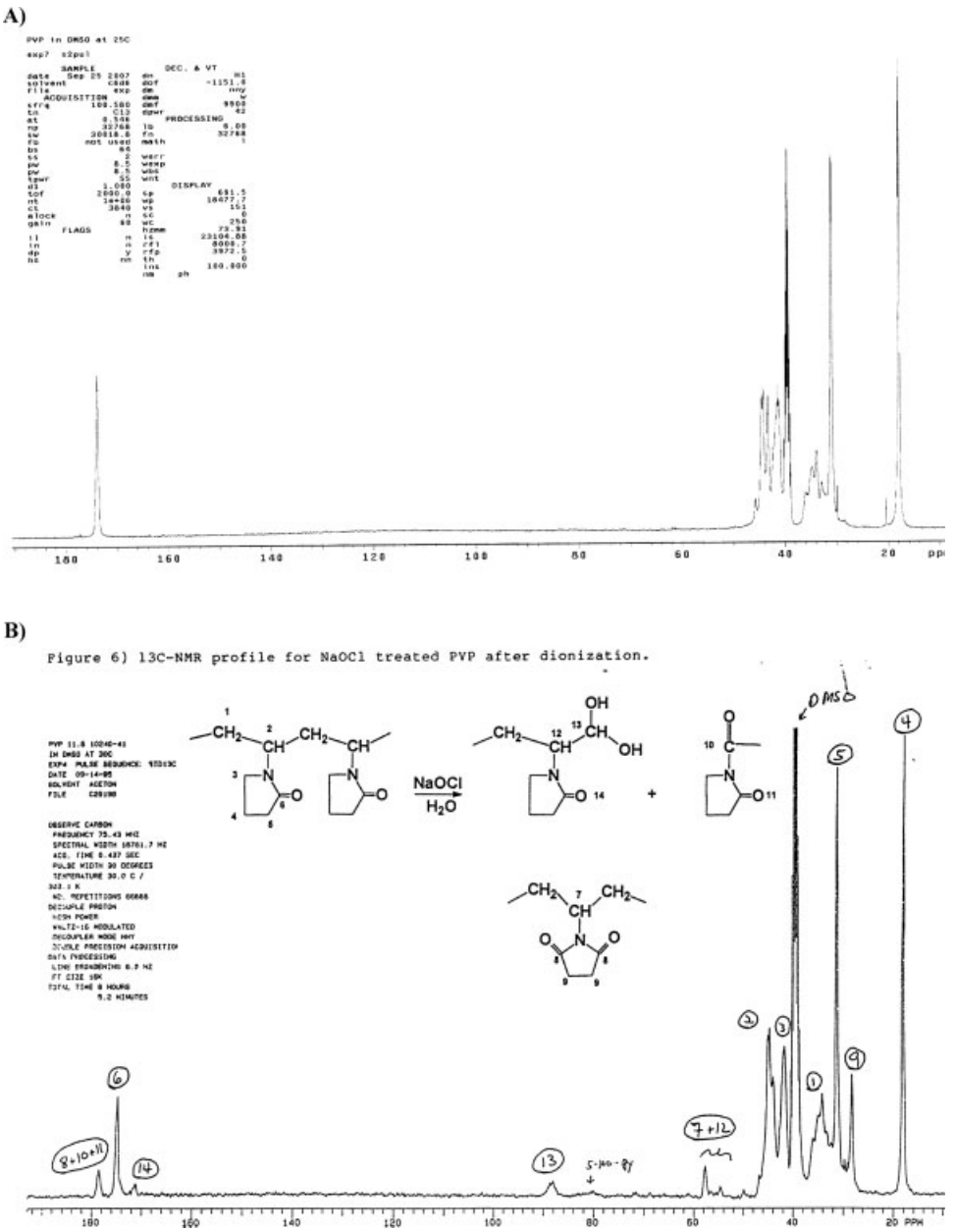

Figure 7 13C-NMR of (A) Untreated PVP and (B) Hypochlorite-treated PVP in DMSO.

which can be degraded by these hydroperoxides and generate impurities of unknown toxicity.[9,10,14,15,16] The two crospovidone materials are only different chemically with respect to the crosslinkers used. We, therefore, hypothesized that the crosslinker used is the cause of this difference in oxidative stability. This conclusion is further supported by the kinetic data obtained.

$$\text{Equation A:} \quad k = Z\, e^{-E_a/RT}$$

$$\text{Equation B:} \quad \ln\, k = \ln\, Z - E_a/RT$$

The Arrhenius equation in its simplest form is depicted as Equation A. The rate of hydroperoxide formation (k) is directly proportional to the pre-exponential Arrhenius factor (Z) that describes the overall collision frequency between reactant molecules (radicals and O_2) as well as the Boltzmann distribution of colliding reactant molecules possessing sufficient energy to reach their transition-states to generate hydroperoxide end-products. E_a is the free-energy required to achieve this transition-state. The temperature dependency to achieve this transition-state is expressed in degrees Kelvin (T), while the thermodynamic constant (R) interrelates energy with temperature.

Using the natural logarithmic form of the Arrhenius equation, Equation B, a straight line can be

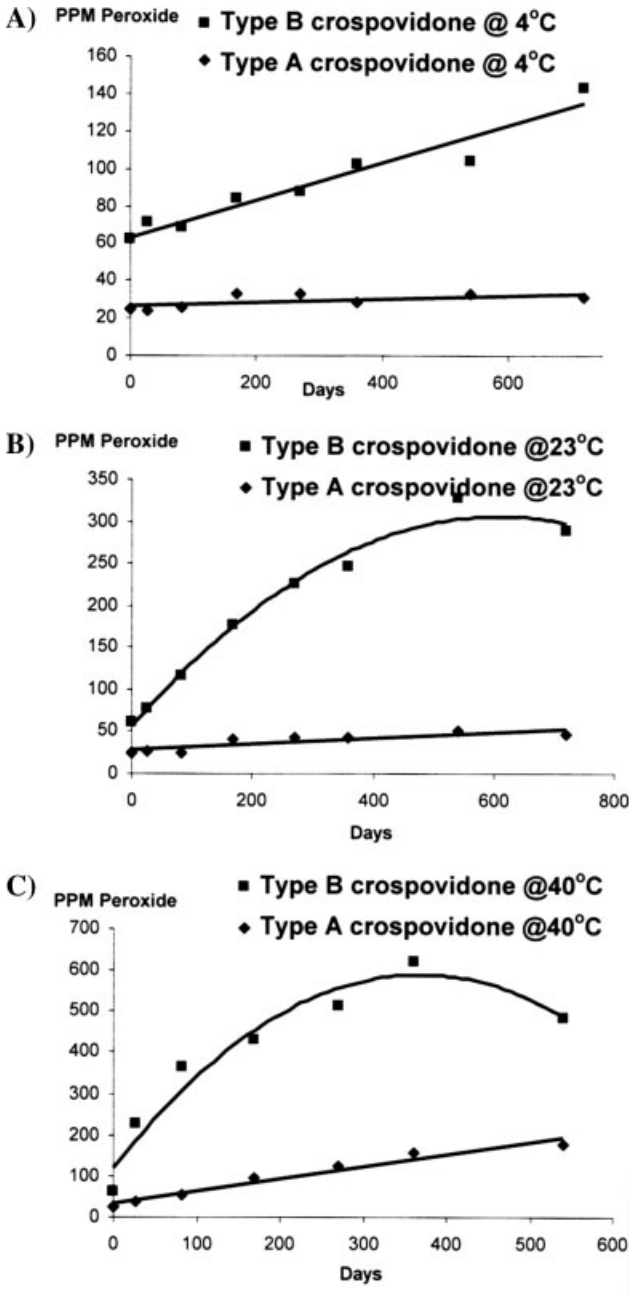

Figure 8 Peroxide buildup study on Type A and Type B crospovidone at (A) 4, (B) 23, and (C) 40°C.

obtained from a plot of ln k versus the reciprocal of the absolute temperature, whereby the slope is $-E_a/R$ and the y-intercept is ln Z. Hence, determining the rate constant for hydroperoxide formation at different temperatures permits the determination of both the energy of activation (E_a) and the collision frequency factor that allow it to reach its transition-state (Z). The data summarizing this analysis for both crospovidone types at 4, 23, and 40°C is summarized in Table II, wherein the values reported are averages of duplicate analyses.

The activation energies and frequency factors for each have been calculated from the hydroperoxide values obtained within the first 270 day period and are also reported in Table II. In particular, at 4°C the Type A crospovidone rate is so slow that it requires at least 270 days to reach a significant hydroperoxide level. In stark contrast, at both 23 and 40°C, the Type B crospovidone rate is so fast that after 169 days and 80 days, respectively, the secondary side-reactions begin to predominate as evidenced by the nonlinear behavior thereafter, Figure 8.

Consequently, the results indicate that Type A and B crospovidones have essentially the same activation energy of 36–41 kJ/mol to reach their transition-states to generate hydroperoxide end-products. Therefore, the two-fold difference observed in their rate constants for hydroperoxide buildup appears to be strictly related to their respective collosion frequencies (Z). The fact that Type B crospovidone has two reactive sites for hydroperoxide buildup on the crosslinker moiety in comparison to that in Type A, Figure 9(A), it further confirms our original hypothesis that the crosslinker used in Type B crospovidone is responsible for the increased rate observed in Type B as compared to Type A. Furthermore, since the rate constant is proportional to a natural logarithmic function, the observed rate for a factor of two with respect to its rate constant results in a 7.4-fold observed increase in hydroperoxide buildup in Type B versus Type A crospovidone.

To reiterate, the Type B process employs nominally 2% *N*,*N*-divinyl imidazolidinone (DVI) as the crosslinker while the Type A process relies upon in situ generated ethylidene vinylpyrrolidinone (EVP) resulting in 1.8–2.5 wt % typically incorporated. The polymerized chemical structures of the two crosslinkers are shown in Figure 9(A). Given the symmetrical nature of the DVI crosslinker, it has twice as many oxygen reactive sites than EVP for hydroperoxide buildup. This is due to the greater ease of hydrogen abstraction at a carbon attached directly to a heteroatom such as nitrogen.[10] This has been demonstrated specifically in a study of free radical reaction at *N*-vinyl-2-pyrrolidinone ring carbon positions. The investigators showed that the 3-position (vicinal to the nitrogen) undergoes the greatest extent of attack (and by a two-fold extent over the next most prone 5-position).[17] To confirm our hypothesis, we evaluated peroxide buildup in model crosslinker analogs that would mimic each particular crosslinker used.

Peroxide buildup in model crosslinker analogs

To simulate the Type B (DVI) crosslinker, we used 1,3-dimethyl-2-imidazolidinone (DMI) as depicted in Figure 9(B). For the Type A (EVP) crosslinker we

TABLE I
Initial Peroxide Buildup in Type A and Type B Crospovidone at 4, 23, and 40°C

Crospovidone type	ppm Peroxide $t = 0$ days	ppm Peroxide $t = 26$ days	ppm Peroxide $t = 83$ days	ppm Peroxide $t = 169$ days	ppm Peroxide $t = 270$ days	ppm Peroxide $t = 360$ days	ppm Peroxide $t = 540$ days	ppm Peroxide $t = 720$ days
Type A at 4°C	25	26	28	33	33	28	33	31
Type B at 4°C	62	71	69	84	88	102	104	144
Type A at 23°C	25	27	28	41	43	43	50	46
Type B at 23°C	62	78	115	178	226	247	328	288
Type A at 40°C	25	37	55	94	123	157	178	–
Type B at 40°C	62	226	365	430	512	621	486	–

used *N*-methyl-2-pyrrolidinone (NMP). Although a 5-methyl substituted-NMP would have been ideal for this study, it was not commercially available nor could it be readily synthesized.

However, if one compares the ambient temperature peroxide buildup rate of Type A (unmilled) crosslinked PVP to noncrosslinked soluble PVP, the crosslinked PVP peroxide buildup rate is actually less than the soluble PVP, Figure 10 and Table II. Care was chosen to compare a spray-dried soluble PVP to the unmilled spray-dried crosslinked PVP, and that the initial hydroperoxide levels were roughly the same before ageing. Therefore, the predominant peroxide buildup site appears to be related to the pyrrolidinone functionality alone, and not to the substituted-pyrrolidinone EVP crosslinker. Hence, the use of NMP to mimic the pyrrolidinone functionality is reasonable. It is also noteworthy that since both analogs are liquids, it is possible to bubble air through them neat, thereby removing any complications due to extraneous solvent effects in the peroxide buildup study of these model compounds.

Illustrated in Figure 11 and summarized in Table III are the initial peroxide buildup rates for the Type B and Type A model crosslinker analogs. As observed in the case of the two crospovidone based materials, increasing the temperature results in increasing the rate of hydroperoxide buildup. More importantly though, the Type B crosslinker analog is dramatically more reactive with oxygen in generating hydroperoxides than the Type A analog at all the temperatures examined, similar to the observation in crosslinked powders.

Interestingly, the initial rates appear to be zero-order at all temperatures examined, identical to those observed with the crospovidone products. With respect to hydroperoxide buildup, the Type B crosslinker analog is not only more reactive to oxygen than the Type A analog, but these data further corroborate our conclusion that the Type B crospovidone product is more susceptible to oxidation due to the crosslinker used to manufacture this product, in comparison to its Type A counterpart.

Furthermore, the temperature dependency of the rate constants for hydroperoxide buildup provides even more convincing evidence. In particular, the Type B model crosslinker analog exhibits a faster rate for hydroperoxide buildup than the Type A, even though the Type B analog also has a higher energy of activation (40 kJ/mol) than the slower Type A (19.7 kJ/mol). Therefore, identical to results obtained with the crosslinked powders, the efficiency of the collision frequency (Z) is solely responsible for the marked difference observed in hydroperoxide buildup rate between these two analogs. Moreover, the relative rate constants of the Type B crosslinker analog are roughly twofold higher than that of the Type A at 45 and 65°C. This finding is clearly consistent with that observed in the crospovidone materials as well.

Moreover, at 65°C the model analog for the Type B crosslinker generates significantly higher levels of hydroperoxides in just a matter of hours. This find-

TABLE II
Initial Peroxide Buildup Rate Constants for Type B vs. Type A Crospovidone

Crospovidone type	Peroxide buildup rate constant at 4°C (277°K)	Peroxide buildup rate constant at 23°C (296°K)	Peroxide buildup rate constant at 40°C (313°K)	Energy of activation (E_a) kJ/mol	Preexponential Arrhenius collision frequency factor (Z)
B	$1.32 \times 10^{-8}\ s^{-1}$	$5.01 \times 10^{-8}\ s^{-1}$	$9.73 \times 10^{-8}\ s^{-1}$	41	$68.3 \times 10^{-2}\ s^{-1}$
A	$0.82 \times 10^{-8}\ s^{-1}$	$2.47 \times 10^{-8}\ s^{-1}$	$4.92 \times 10^{-8}\ s^{-1}$	36	$5.3 \times 10^{-2}\ s^{-1}$
Source 1 soluble PVP K-90	–	$3.03 \times 10^{-8}\ s^{-1}$	–		

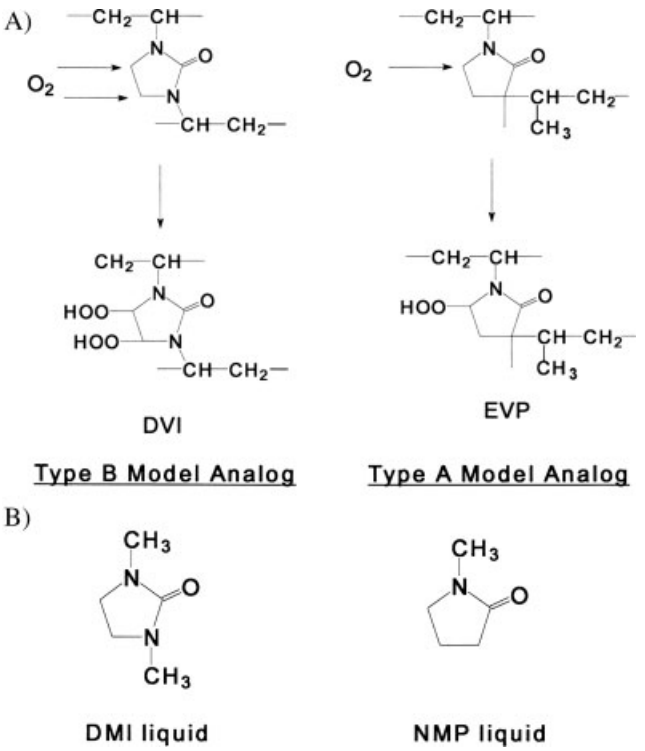

Figure 9 (A) Chemistry of peroxide buildup for Type B and Type A crosslinkers in crospovidone. (B) Chemical structures for Type B and Type A model crospovidone crosslinker analogs.

ing is noteworthy since at the spray-dryer nozzle that is operated at 100+°C in air, it would be expected that Type B crospovidone would generate a higher initial level of hydroperoxide than Type A.

CONCLUSIONS

The results obtained have demonstrated that when one compares Type A with Type B crospovidone the peroxide buildup rate is significantly higher in the Type B crospovidone by at least a factor of two when compared to its Type A counterpart at ambient temperature or above. Furthermore, as the temperature increases, so does the rate of formation of hydroperoxides.

These findings would indicate that the Type B crospovidone material has an inherent feature which causes the rate of buildup and level of hydroperoxide reached under identical conditions to be greater than the Type A counterpart. These two materials are only different chemically with respect to the crosslinkers used. Corroborative spectroscopic data that the pyrrolidinone ring is further oxidized to the

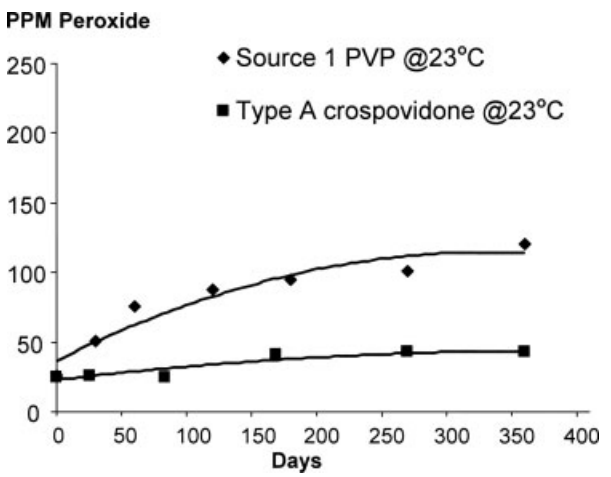

Figure 10 Relative peroxide buildup rates for soluble PVP vs. Type A crospovidone at 23°C.

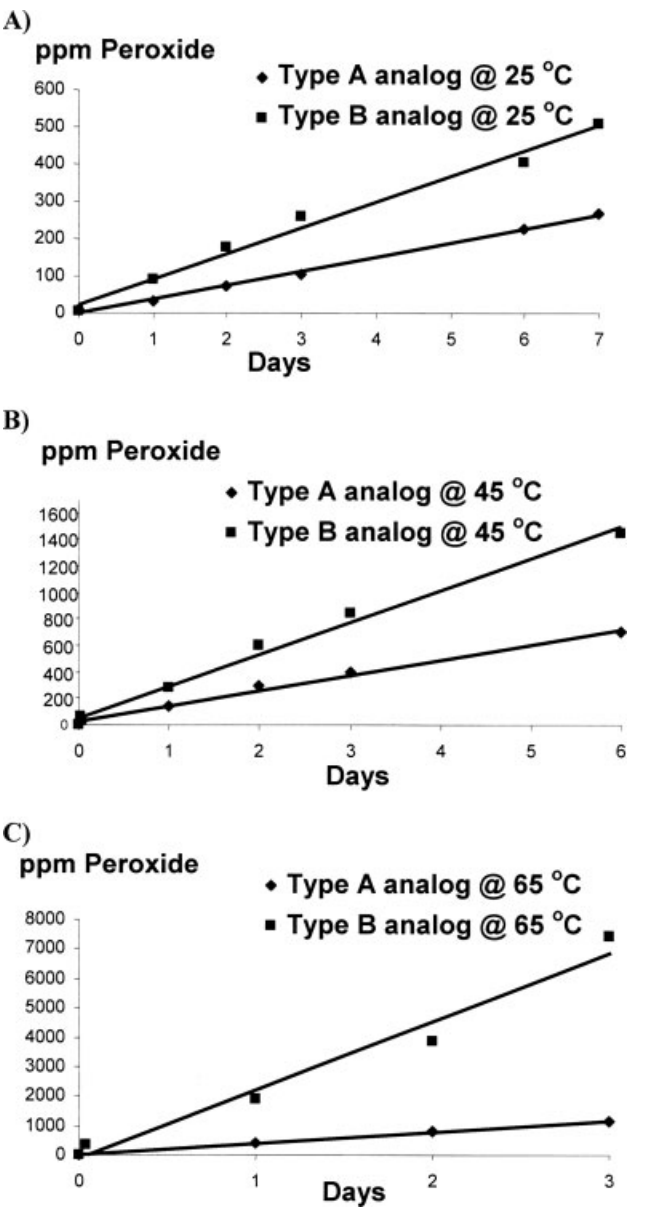

Figure 11 Peroxide buildup study on model crosslinker analogs at (A) 25, (B) 45, and (C) 65°C.

TABLE III
Initial Peroxide Buildup Rate Constants for Type B vs. Type A Model Crosslinker Analogs

Model crosslinker analog	Peroxide buildup rate constant at 25°C (298°K)	Peroxide buildup rate constant at 45°C (318°K)	Peroxide buildup rate constant at 65°C (338°K)	Energy of activation (E_a) kJ/mol	Preexponential Arrhenius collosion frequency factor (Z)
Type B	4.16×10^{-6} s^{-1}	11.56×10^{-6} s^{-1}	14.09×10^{-6} s^{-1}	40.2	46.2 s^{-1}
Type A	3.72×10^{-6} s^{-1}	6.14×10^{-6} s^{-1}	6.41×10^{-6} s^{-1}	19.7	1.1×10^{-2} s^{-1}

succinimide functionality over time has also been presented. Additionally, the drying process can have a significant impact in the rate of hydroperoxide buildup within these types of polymers. Since both types of crospovidone are dried and post-processed in the same fashion, the difference observed between the Type A and Type B crospovidone should be related to their chemical composition instead. The kinetic data reveal that the difference in the rate of hydroperoxide buildup between these two crospovidone materials is entirely related to the efficiency of the collisions between polymer and oxygen to reach its transition-state to generate hydroperoxide end-products. Therefore, the crosslinker used in Type B crospovidone appeared to be responsible for the significant difference observed in hydroperoxide level observed over time, when compared to its Type A counterpart.

The model crosslinker analog study was found to support the observed differences in hydroperoxide formation between Type A and Type B crospovidones. In particular, the Type B model crosslinker analog is significantly more reactive to oxidation than the Type A analog. Similar to the crospovidone results, increasing the temperature results in increased hydroperoxide formation. This rate of increase is significantly higher for the Type B model crosslinker analog than its Type A analog. It was not surprising that the rate constants for the crospovidone samples compared to their respective crosslinker analogs were different, given the fact that oxidation of crospovidone is a solid-gas reaction, while the crosslinker analogs is a liquid-gas reaction. This is further supported by the 100-fold difference in their respective rate constants observed between the crosslinker analogs and the crospovidone products. However, directionally the Type B crosslinker analog was still the most reactive as expected.

More importantly, the kinetic data for the model crosslinker analogs further confirm that the difference observed between these two products is primarily due to the crosslinker used in Type B crospovidone when compared to Type A. In particular, the results of the model crosslinker analogs study demonstrate that the Type B analog exhibits a significantly higher rate of hydroperoxide buildup over time. This difference is essentially related to the difference in collision efficiency between the respective chemical structures and oxygen. Hence, the marked difference observed between these two disintegrants is entirely related to the crosslinkers used.

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