Pharmaceutical Research, Vol. 15, No. 7, 1998

Effect of Hydrogen Peroxide on the Viscosity of a Hydroxyethylcellulose-Based Gel

Terry Dahl,[1] Gong-Xin He,[1,2] and Glenn Samuels[1]

Received January 16, 1998; accepted March 24, 1998

KEY WORDS: gel; hydroxyethylcellulose; hydrogen peroxide; viscosity; oxidative degradation; antioxidants; packaging.

INTRODUCTION

Peroxides can be found in trace levels in many pharmaceutical excipients. These peroxide impurities in turn can cause chemical degradation of these excipients and active ingredients susceptible to oxidative degradation. Several studies have shown that polyglycols and certain ether-based surfactants may contain peroxides generated through autooxidation of these materials (1–5). For example, Johnson and Taylor showed that peroxide impurities generated through the autooxidation of polyethylene glycol in the formulation can affect the stability of fenprostalene and adding an antioxidant, such as *dl*-α-tocopherol, to the formulation can improve the stability (2).

Oxidative degradation of cellulose ether derivatives has been reported in the nonpharmaceutical literature (6–9). For example, latex paint is prepared through a polymerization process using a redox-type initiator, but also contains cellulose ether derivatives as a thickener. The oxidative/reductive substances coming from the initiator, such as hydrogen peroxide, were shown to be capable of causing viscosity loss of the final latex paint (7).

Currently, there are no reports on the oxidative degradation of cellulose ether derivatives in pharmaceutical formulations, even though cellulose ether derivatives are very common excipients for oral, topical, ophthalmic, and vaginal formulations. For example, hydroxypropylmethylcellulose and hydroxyethylcellulose (HEC), which are cellulose ether derivatives, are widely used as a viscosity enhancer for vaginal and topical gel products.

The purpose of this study is to investigate the effect of hydrogen peroxide on the viscosity of a topical gel product using HEC as a thickener. In the first part of this study, hydrogen peroxide was spiked into a previously prepared gel by mixing the gel with an aqueous solution of hydrogen peroxide or was added as a formulation component during the manufacture of the gel. The viscosity of the gel and the concentration of the hydrogen peroxide in the gel were monitored for 2 months. In the second part of the study, eighteen batches of the model gel were prepared according to an experimental design to investigate the effects of hydrogen peroxide concentration, antioxidant concentration, and packaging system on the viscosity of the gel product as a function of storage time.

EXPERIMENTAL SECTION

Materials

All chemical reagents were purchased from Aldrich (Milwaukee, WI). Milli-Q water was used in the experiments.

Drug substance (Lot No. 1966-C-4) was supplied by Gilead Sciences (Foster City, California). Hydroxyethylcellulose (NF, Natrosol 250H, Lot No. 35793 and FP10 12437) was obtained from Aqualon (Wilmington, Delaware). Other excipients, such as propylene glycol (USP, Lot No. KG402), hydrogen peroxide, 30% aqueous solution, (ACS, Lot No. KB024), and butylated hydroxyanisole (USP, Lot No. JC528) used in the experiments were purchased from Spectrum Chemicals (Gardena, California).

The gel was packaged either in glass vials (5 mL) capped with a Teflon-coated 20-mm gray butyl rubber stopper (Wheaton, Millville, New Jersey) or in epoxy-lined aluminum tubes (blind end, 0.5″ diameter × 2.625″ length, Lot No. JT994).

Methods

Preparation of HEC Gel

The gel was prepared by combining an aqueous portion and an organic portion using a homogenizer. The aqueous portion was prepared by dissolving the active ingredient and other water-soluble components in water. The organic portion contained HEC, propylene glycol, and preservatives. The aqueous portion was adjusted to a pH value of 6.9 ± 0.2 before combining the two portions. Processing parameters were the same for all batches.

The bulk gel obtained was allowed to deaerate for 24 hours at room temperature. Sampling of the bulk gel was conducted from the top, middle, and bottom locations of the mixing vessel. The viscosity values of the gel samples were measured and the relative standard deviation (RSD) was calculated. The RSD for bulk gel sampled from different locations was less than 6%, indicating a good homogeneity.

Addition of Hydrogen Peroxide to a Pre-Prepared HEC Gel

Three grams of the gel product prepared through the procedure described in *Preparation of HEC gel* were weighed in a 20-mL glass vial. After adding 100 μL of 0.06% w/w or 0.6% w/w aqueous hydrogen peroxide solution prepared from the 30% w/w aqueous hydrogen peroxide solution, the vial was capped and sealed. The vial was then shaken with a Vortex mixer for 1 minute. A total of 24 samples were prepared and stored at 30°C. Twelve samples contained 20 ppm of hydrogen peroxide and twelve contained 200 ppm. The viscosity was determined using the viscometer. The hydrogen peroxide concentration was determined using the iodometric titration. Both viscosity and hydrogen peroxide concentration were monitored at 6 time points over a total time period of 42 days. All results were reported as the average value from two samples.

Addition of Hydrogen Peroxide as a Formulation Component when Preparing an HEC Gel

The gel product was prepared with the method described in *Preparation of HEC gel* except for adding hydrogen peroxide

---

[1] Formulation and Process Development, Gilead Sciences, Inc., 333 Lakeside Drive, Foster City, California 94404.

[2] To whom correspondence should be addressed. (e-mail: gong-xin_he@gilead.com)

to the aqueous portion, prior to combining with the organic portion, to achieve concentrations of 0, 15, and 50 ppm for the hydrogen peroxide in the final HEC gel. Three grams of the gel were weighed in a 20-mL glass vial. The vial was capped, sealed, and then stored at 30°C. The viscosity and the hydrogen peroxide concentration were monitored for a period of 64 days.

Measurement of the Viscosity of HEC Gel

A viscometer (RVDV-III, Brookfield), equipped with a cone type spindle (CP-52) and water-jacketed sample cup, was used to measure the viscosity of the HEC gel. The parameters used were as follows. Temperature = 30 ± 0.5°C; spindle rotation speed = 8 rpm (equal to a shear rate of 16 sec^{-1}); sample size = 0.5 mL. The initial viscosity of the HEC gel ranged from 7500–8500 cP and the RSD for the viscosity measurement was ≤ 10%. In this paper, the viscosity change was reported as a viscosity loss in the percentage of the initial viscosity.

Determination of the Hydrogen Peroxide Concentration in HEC Gel

One gram of HEC gel was weighed and dissolved into 5 mL of distilled water. Aqueous 0.1 N potassium iodide solution was prepared by dissolving 1.66 g of potassium iodide in 100 mL of water. One mL of the potassium iodide solution and 2 mL of 1 N sulfuric acid were added to the diluted aqueous solution of the HEC gel. The resulting solution was stirred at room temperature for 15 minutes. After adding 1 mL of the starch indicator solution, the solution obtained was titrated with 0.01 N aqueous sodium thiosulfate solution using a pipetman (5 μL or 20 μL increments) until the blue color disappeared (10,11). The RSD for the analysis from two samples was ≤ 5%.

Experimental Design Evaluation for the Effect of Hydrogen Peroxide on Gel Viscosity

Eighteen batches of the HEC gel were prepared according to an experimental design generated with a software package (JMP, Version 3.1, SAS Institute Inc., Cary, North Carolina).

The HEC gel was prepared with the method described in *Preparation of HEC Gel* except for adding certain amounts of hydrogen peroxide and butylated hydroxyanisole to the aqueous portion and the organic portion, respectively, before the mixing. The gel was prepared from two different lots (Lot No. 35793 and FP10 12437) of HEC, contained three levels (0, 15, and 50 ppm) of hydrogen peroxide and three levels (0, 100, and 200 ppm) of butylated hydroxyanisole.

All eighteen batches of the gel were filled into two packaging systems and contained a net fill weight of 3 g. Twelve of the eighteen batches were packaged into glass vials. Six batches were packaged into epoxy-lined aluminum tubes. The gel was stored at 30 ± 1°C during the 6-month experiment. The first viscosity measurement was conducted 7 days after the gel was prepared. The samples were tested for viscosity at 0, 1, 3, and 6 months storage time.

RESULTS AND DISCUSSION

Effect of the Hydrogen Peroxide on the Gel Viscosity

As shown in Figures 1 and 2, hydrogen peroxide caused a rapid and significant decrease in the viscosity of the HEC gel, regardless of whether the hydrogen peroxide was added either during or after the gel preparation. Concurrent with the loss of viscosity, the concentration of the hydrogen peroxide in the gel also decreased. Once the hydrogen peroxide concentration decreased to an undetectable level (< 1 ppm), the viscosity of the gel stabilized. In contrast, the sample containing $[H_2O_2]_{initial}$ = 200 ppm (Figure 1) had 60 ppm of hydrogen peroxide remaining at the end of the experiment, and the slope of the viscosity loss remained positive. These results strongly correlate the viscosity loss of the gel to the quantity of the hydrogen peroxide present.

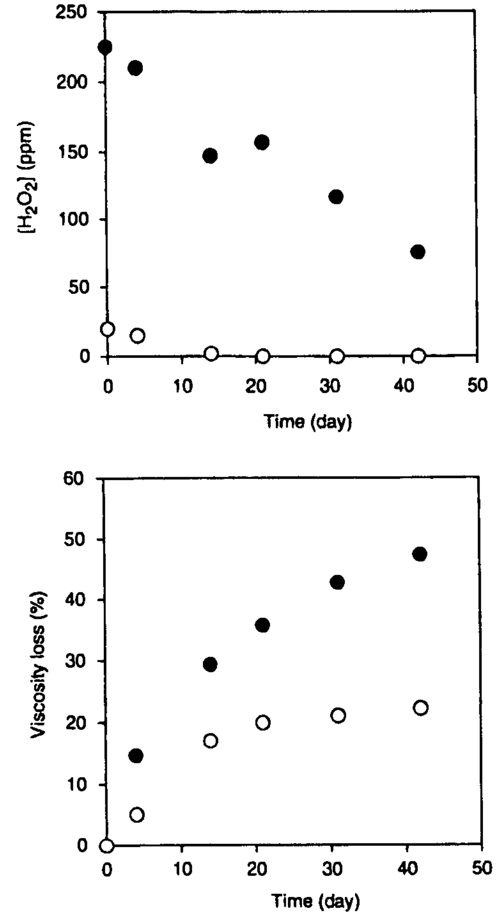

Fig. 1. Changes in the concentration of hydrogen peroxide (top) and the viscosity of the HEC gel (bottom) as a function of time after adding the hydrogen peroxide to a previously prepared gel. Open circle: $[H_2O_2]_{initial}$ = 20 ppm, solid circle: $[H_2O_2]_{initial}$ = 200 ppm.

Hydroxyethylcellulose contains many C-H bonds that can be subjected to radical-mediated oxidation (Figure 3). These C-H bonds are oxidized in a stepwise process leading to the hydroperoxide products (C-OO-H) (12). Decomposition of the hydroperoxide formed at the acetal C-H shown in Figure 3 can cleave the main polymer chain (13) and cause a significant decrease in the gel viscosity. Decomposition of the hydroperoxides formed at other positions, such as the ether C-H or the alcohol C-H shown in Figure 3, can cause cleavage of the side chain or can disrupt the inter-chain hydrogen bonding, consequently affecting the viscosity. A study conducted in the paper industry showed that oxidation with 5% hydrogen peroxide can cause significant degradation of cellulose-based paper

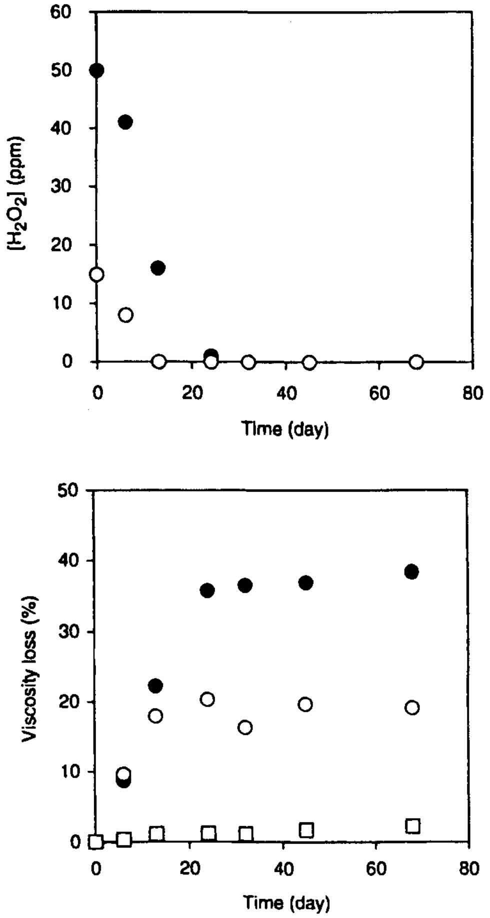

Fig. 2. Changes in the concentration of hydrogen peroxide (top) and the viscosity of the HEC gel (bottom) as a function of time after adding the hydrogen peroxide as a gel component in the preparation of the gel. Open square: $[H_2O_2]_{initial}$ = 0 ppm, open circle: $[H_2O_2]_{initial}$ = 15 ppm, solid circle: $[H_2O_2]_{initial}$ = 50 ppm.

and that the ratio of the oxidative cleavage, occurring at the ether or alcohol C-H to that at the acetal C-H in cellulose, ranges from 3:1 to 4:1 (14). Rapid but limited degradation caused by hydrogen peroxide and iron(II) sulfate has been reported for a gel based on crosslinked hyaluronic acid, which has a polymeric structure similar to cellulose (15).

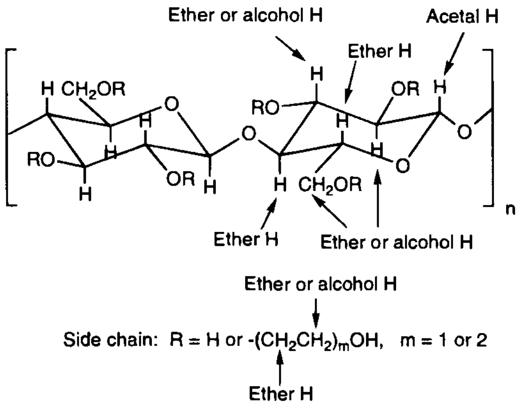

Fig. 3. Possible oxidation sites on hydroxyethylcellulose.

Evaluation of the Factors Capable of Affecting on the Gel Viscosity

The viscosity of 18 batches of the gels, comprised of two different lots of the HEC raw material, two different package systems, and three levels of hydrogen peroxide and butylated hydroxyanisole, was monitored for 6 months.

The viscosity changes for the gel product made from the two different lots of the HEC raw material were almost identical, except for small differences in the initial viscosity. Moreover, the results obtained from the gel packaged in epoxy-lined aluminum tubes (data not shown) are basically the same as those for the gel packaged in glass vials. The epoxy lining material did not affect the viscosity of the gel with or without hydrogen peroxide. The performance of the antioxidant was equivalent for the gel packaged in either glass vials or epoxy-lined aluminum tubes. Therefore, only one three-dimensional plot of the results obtained from the gel, made from one lot (Lot No. 35793) of HEC and packaged in glass vials, is shown in Figure 4.

Figure 4 illustrates that addition of hydrogen peroxide to the gel can cause a rapid decrease in the gel viscosity. In the figure, a viscosity loss ($< 10\%$) at the initial time point ($t = 0$) is due to the artificial effect of the regression equation used to model the data points collected in this study. As shown in the figure, when the gels containing no hydrogen peroxide were stored at 30°C for 6 months, the viscosity loss was less than 10%. However, for the gels containing 50 ppm hydrogen peroxide, the viscosity loss was greater than 40%.

In this study, butylated hydroxyanisole (BHA) was added to an HEC gel to investigate the effect of an antioxidant on the gel viscosity with or without hydrogen peroxide. BHA is widely used as an antioxidant in many pharmaceutical products with a concentration up to 200 ppm for topical formulations and has the high aqueous solubility necessary for processing an aqueous gel (16). The control gel showed that adding BHA to the HEC gel without hydrogen peroxide caused no viscosity change in the gel. As shown in Table I, adding BHA to the HEC gel reduced the effect of the hydrogen peroxide on the gel viscosity, but the inhibitory effect was not significant up to an antioxidant concentration of 200 ppm. It was also found that all gel samples containing $[H_2O_2]_{initial}$ = 50 ppm and $[BHA]_{initial}$ = 200 ppm

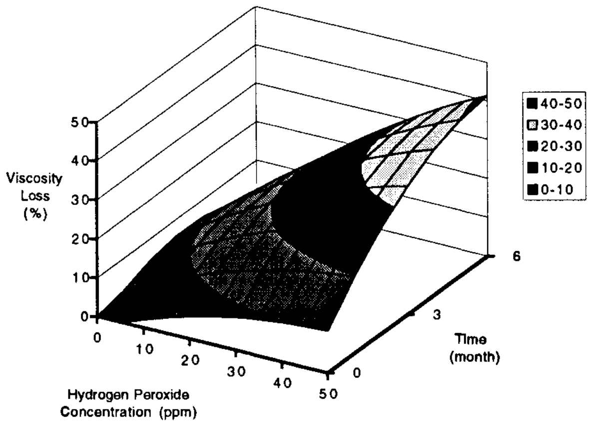

Fig. 4. Changes in the viscosity of the HEC gel packaged in glass vials and containing 0 ppm of BHA as functions of time and initial hydrogen peroxide concentration after adding the hydrogen peroxide and BHA as gel components.

Table I. Inhibitory Effect of BHA on the Viscosity Loss of the HEC Gel When $[H_2O_2]_{initial}$ = 50 ppm

$[BHA]_{initial}$ in ppm	0	100	200
Viscosity loss (%)			
t = 1 month	33	23	21
t = 3 months	36	28	27
t = 6 months	42	38	36

were cloudy and pale-yellow colored after storage at 30°C for 6 months, suggestive of BHA oxidation products. From this observation, we conclude that the radical chain reaction is extremely efficient and selective in the HEC gel system, and these levels of BHA are not sufficient to suppress completely the oxidative degradation of HEC in the gel. In fact, it was reported that the oxidative degradation of a cellulose triacetate film caused by hydroperoxides can be suppressed only by using a combination of two or more different antioxidants (6). Therefore, special attention is needed to avoid the contamination of a cellulose ether based gel product with hydrogen peroxide or any other oxidant.

CONCLUSIONS

A trace amount of hydrogen peroxide can cause a rapid and significant decrease in the viscosity of a hydroxyethylcellulose-based gel product. Once the hydrogen peroxide concentration decreases to an undetectable level, the change in the gel viscosity stabilizes or may decrease at a much lower rate over a relatively long time period. Although adding butylated hydroxyanisole (BHA) to the HEC gel containing hydrogen peroxide can reduce the viscosity loss of the gel, the inhibitory effect is not significant even with up to 200 ppm of the antioxidant.

REFERENCES

1. E. Azaz, M. Donbrow, and R. Hamburger. Incompatibility of nonionic surfactants with oxidizable drugs. *Pharm. J.* **211**:5723–5723 (1973).
2. D. M. Johnson and W. F. Taylor. Degradation of fenprostalene in polyethylene glycol 400 solution. *J. Pharm. Sci.* **73**:1414–1417 (1984).
3. J. W. McGinity, J. A. Hill, and A. L. LaVia. Influence of peroxide impurities in polyethylene glycols on drug stability. *J. Pharm. Sci.* **64**:356–357 (1975).
4. D. S. Bindra, T. D. Williams, and V. J. Stella. Degradation of O^6-Benzylguanine in aqueous polyethylene glycol 400 (PEG 400) solutions: Concerns with formaldehyde in PEG 400. *Pharm. Res.* **11**:1060–1064 (1994).
5. B. J. Tyler and B. D. Ratner. Oxidative degradation of Biomer™ fractions prepared by using preparative-scale gel permeation chromatography. *J. Biomater. Sci. Polymer Edn.* **6**:359–373 (1994).
6. N. S. Allen, M. Edge, and T. S. Jewitt. Degradation and stabilization of cellulose triacetate base motion picture film. *J. Imaging Sci. and Tech.* **36**:4–12 (1992).
7. H. Winters and M. Goll. Nonenzymatic oxidative degradation of hydroxyethyl cellulose thickened latex paints. *Journal of Coatings Technology* **48**:80–85 (1976).
8. V. L. Irwin and M. M. Williams. Viscosity loss in hydroxyethylcellulose thickened latex paints caused by chemical oxidants: Method of detection. *Journal of Coatings Technology* **52**:71–74 (1976).
9. European Patent Application, High Solids Low Viscosity Polysaccharide Composition, No. 0465992 A1. Aqualon Co., February 7, 1991.
10. Assay for Oxidizing Substances Present in Propylene Glycol, BP, 1993, Vol. 1, HMSO, London, p. 556.
11. The method using potassium permanganate titration described in USP (Monograph for Hydrogen Peroxide Concentrate, USP 23, 1995, Rand McNally, Taunton, MA, p. 767) is not suitable for the gel system, since the permanganate is able to oxidize the organic components present in the gel.
12. L. F. McBurney. Degradation of cellulose. In E. Ott, H. M. Spurlin, and M. W. Grafflin (eds.), *Cellulose and Cellulose Derivatives. Part I*, Interscience, New York. 1954, p. 99.
13. E. M. Kuramshin, L. G. Kulak, M. N. Nazarov, S. S. Zlotskii, D. L. Rakhmankulov. Oxidation of cyclic acetals as a preparation method of diol monoester production. *J. Prakt. Chem.* **331**:591–599 (1989).
14. P. M. Whitmore, J. Bogaard. Determination of the cellulose scission route in the hydrolytic and oxidation degradation of paper. *Restaurator* **15**:26–45 (1994).
15. N. Yui, T. Okano, Y. Sakura. Inflammation responsive degradation of crosslinked hyaluronic acid gels. *J. Controlled Release* **22**:105–116 (1992).
16. Monograph for Butylated Hydroxyanisole (BHA). In A. Wade and P. J. Weller (eds), *Handbook of Pharmaceutical Excipients*, 2nd Ed., American Pharmaceutical Association and the Pharmaceutical Press, 1994, p. 45.