Effects of Shear Processing and Thermal Exposure on the Viscosity-Stability of Polymer Solutions

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The effects of high-shear processing and thermal exposure on the molecular weight and solution viscosity stability of selected polymers were studied. Aqueous solutions of two molecular weight grades of hydroxyethyl cellulose (HEC) were subjected to high-shear rates using a high-shear mixer and two colloid mills. Extremely rigorous shearing conditions were required to alter the viscosity. The viscosity stability of the two grades of HEC was studied under prolonged thermal treatment at 70°. Viscosity degradation was found to follow a first-order reaction rate, the viscosity half-life for the higher grade being considerably less than that for the lower molecular weight grade. Number-average molecular weights for the HEC's were determined by the osmotic pressure technique and related to viscosity-average molecular weights through intrinsic viscosity data. The correlation between the two types of molecular weights was high, implying that bond-scissions and hydrolysis were the cause of viscosity degradation.

THE PHYSICAL nature of most pharmaceutical dispersed systems necessitates the use of viscosity imparting agents or dispersing aids to reduce phase separation tendencies, thereby enhancing medicament distribution. Virtually all such agents are polymeric in structure and fall under the general categories of natural gums, resins, and synthetic polymers. The latter group finds the most application in present-day suspension technology. The viscosity imparted to a system by the presence of these solvated polymeric agents is dependent on their spacial configurations in colloidal solution which is primarily a function of molecular weight, and to some extent, the degree of substitution or branching along the polymer chains.

Various physicochemical forces are capable of randomly rupturing the long chain structure of high molecular weight polymers (1). Two physical forces which may initiate depolymerization and subsequent viscosity loss in high polymer systems are mechanical shear and thermal energy. Studies (2–4) have shown that mechanical depolymerization of polymers in solution may occur and that this phenomenon is difficult to quantify. In most instances, the degradation reactions approximate the first-order rate law. Factors contributing to this mechanical phenomenon include (a) shear rate, (b) the average molecular weight of the polymer, (c) polymer–solvent interactions, and (d) the stereochemistry of the polymer and solvent. With polymer systems containing suspended particles, the concentration and particle size characteristics of the suspended material may affect the total shear within the system to provide an added factor influencing mechanical depolymerization (5).

The effect of temperature upon the viscosity stability of aqueous solutions of several hydrophilic polymers has been studied (6–8). While some workers (9, 10) suggest that viscosity reduction with prolonged heating is due to actual depolymerization or hydrolysis, Caldwell and Watters (11) contest the occurrence of any structural changes. A permanent viscosity decrease of a polymer solution should not be taken as absolute evidence of depolymerization, since this effect may be due to deaggregation and/or desolvation of the polymer.

This study was initiated to investigate the viscosity stability of certain hydrophilic polymers under conditions allied with the manufacture and production of pharmaceutical dispersions.

EXPERIMENTAL

Polymer Selection and Solution Preparation.— Two molecular weight grades of hydroxyethyl cellulose,[1] HEC-250G and HEC-250H, were used in this investigation. According to the manufacturer, the approximate molecular weights are 80,000 and 210,000, respectively; however, the method by which these values were obtained was not stated. These polymers were used as received from the manufacturer. The moisture content was determined and used in calculating the necessary weight of material to be used for preparing the required solutions.

Aqueous solutions (w/v) were prepared by dispersing the finely powdered polymers in distilled water at 5° with the aid of a magnetic stirrer. Stirring was then continued until the dispersions reached room temperature and solution had occurred. Generally 4–8 hr. were required. The solutions were made up to volume and allowed to hydrate for a minimum of 24 hr. before being used.

[1] Natrosol 250G and 250H, Hercules Powder Co., Wilmington, Del.

TABLE I.—MILLING OPERATIONS ON HEC SOLUTIONS

Viscosity Grade	Concn., %, w/v	Vol. Milled, ml.	Power Equip.	r.p.m. and Gap	Shear Rate,[a] sec.[-1]	Shear Time, min.
250H	1.0	1000	EHM[b]	8500–9000	. . .	5.5
250H	1.0	1000	EHM	11,000–11,500	. . .	5.0
250H	1.0	850	MGCM[c]	18,000 0.001 in.	1.88×10^6	90[e]
250H	1.0	1500	THCM[d]	11,000 0.002 in.	6.87×10^5	One pass
250G	2.0	900	EHM	8650–8950	. . .	5.0
250G	4.0	900	MGCM	18,000 0.002 in.	9.44×10^5	12.0

[a] The approximate shear rate for colloid mills was determined by the following equation given by Kostenbauder *et al.* (12): S = rotor peripheral velocity/rotor-stator clearance. [b] Eppenbach Homo mixer, model 1-L, Gifford Wood Co., New York, N. Y. [c] Manton-Gaulin colloid mill, model 2B, Manton-Gaulin Manufacturing Co., Everett, Mass. [d] Tri-Homo colloid mill, Tri-Homo Corp., Salem, Mass. [e] The temperature of the solution was maintained at 20°.

Viscosity Analysis.—Intrinsic viscosities were determined for both grades of HEC using a Cannon-Fenske No. 200[2] capillary viscometer at a constant temperature of 25 ± 0.01°. The viscometer was standardized with a 20-ml. sample of distilled water, and the mean solvent efflux time was determined. Efflux times for 20-ml. samples of five dilute solutions of HEC-250G (0.04–0.2 Gm./100 ml.) and HEC-250H (0.01–0.1 Gm./100 ml.) were determined and the respective relative viscosities (η rel.) calculated. By converting (η rel.) to reduced specific viscosities (η sp/c), and plotting these values against concentration, the intrinsic viscosities were obtained by extrapolation to infinite dilution.

Pseudoplastic rheograms of the HEC solutions at 25° were obtained using a Ferranti-Shirley[3] plate and cone viscometer. The instrument was calibrated with N.B.S. oil M[4] using the 2.75-in. diameter cone throughout.

Molecular Weight Determination.—Number-average molecular weights for both grades of HEC were determined in water at 25 ± 0.01° using a Stabin-Immergut[5] bi-membrane osmometer. Regenerated cellulose films No. 300[6] were used as the semipermeable membranes. Five different concentrations of each polymer were used to determine osmotic pressures which were corrected for membrane asymmetry. Corrected pressures were converted to reduced osmotic pressures which were plotted against concentration. The graphs were extrapolated to infinite dilution and the molecular weights were calculated by the following equation:

$$M\bar{n} = \frac{RT}{(\pi/c)_c = 0} \quad \text{(Eq. 1)}$$

where $M\bar{n}$ = number-average molecular weight,
R = gas constant (L. Atm. mole[-1] degree[-1]),
T = absolute temperature,
$(\pi/c)_c = 0$ = reduced osmotic pressure at infinite dilution.

Shear Depolymerization.—Aqueous polymer stock solutions were subjected to varying degrees of

agitation and hydrodynamic shear imparted by the use of power equipment common to the pharmaceutical industry (Table I.)

Thermal Depolymerization.—The effects of thermal exposure on the viscosity and molecular weight of 2.0% HEC-250G and 1.0% HEC-250H in solution were investigated. The viscosity stability of solutions of the polymer samples at room temperature was also observed.

Six 135-ml. samples of each polymer stock solution were placed individually in 8-oz. dark glass bottles which were then tightly sealed and placed in a dry air oven at 70 ± 1°. Samples were periodically removed from the oven over a 12–13-day interval and assayed viscometrically. A 1000-ml. sample of HEC-250G (2.0%) was treated at 70° for 48 hr. In addition to assaying this sample viscometrically, the number-average molecular weight was determined.

RESULTS

Mechanical Shear Effects.—Viscosity and molecular weight loss were indicated in only the 90-min. milling operation where a 1.0% HEC-250H solution was allowed to recycle through the rotor-stator mechanism of the Manton-Gaulin colloid mill (Table I).
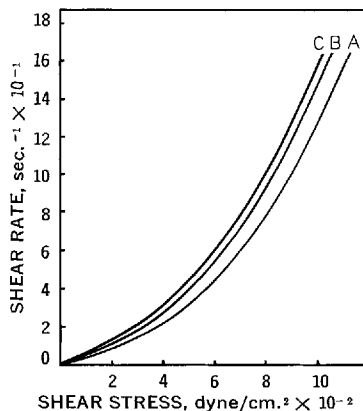

Fig. 1.—Pseudoplastic flow of HEC-250H (1% w/v) milled for 90 min. in the Manton-Gaulin colloid mill. Key: A, initial; B, 30, 45, and 60-min. samples; C, 75 and 90-min. samples.

[2] Cannon Instrument Co., State College, Pa.
[3] Ferranti-Shirley Co., Manchester, England.
[4] National Bureau of Standards, Washington, D. C.
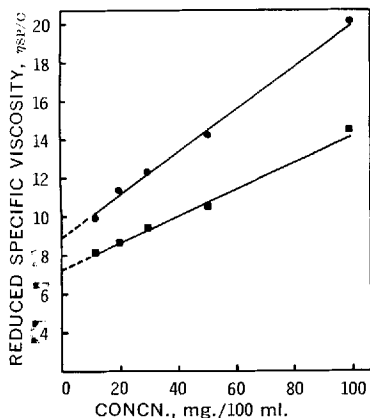[5] J. V. Stabin, Brooklyn, N. Y.
[6] FMC Corp., Fredericksburg, Va.

Fig. 2.—Reduced specific viscosity of HEC-250H before and after 90 min. of milling. Key: ●, initial $[\eta] = 8.7$; ■, after 90 min. $[\eta] = 7.5$.
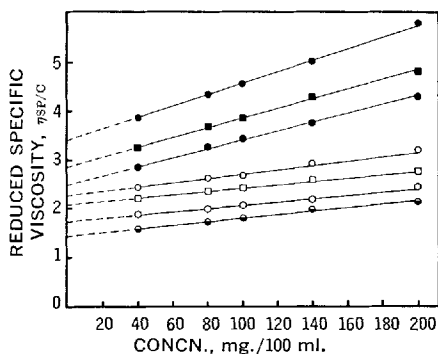

Fig. 3.—Reduced specific viscosity of HEC-250G solutions (2% w/v) thermally degraded at 70°. Key: ●, initial; ■, 24 hr.; closed hexagon, 48 hr.; ○, 94.5 hr.; □, 144 hr.; ◇, 192 hr.; ◐, 300 hr.

Samples were removed after 30 min. and at 15-min. intervals thereafter and evaluated on the Ferranti-Shirley viscometer (Fig. 1). The reduction in shear stress at a shear rate of 1.66×10^3 sec.$^{-1}$ was 6% for the 30, 45, and 60-min. samples and 9.1% for the 75 and 90-min. samples. The bulk solution remaining after 90 min. was used to determine intrinsic viscosity (Fig. 2). The reduction in intrinsic viscosity was 15%.

Thermal Exposure Effects.—Preliminary studies indicated that the intrinsic viscosity of HEC-250G (2.0%) did not vary over an 18-day period at room temperature. Therefore, any change in the intrinsic viscosity of HEC solutions at elevated temperatures would be solely a function of the heat conditions used as opposed to any spontaneous viscosity change at room temperature.

The effects of temperature with time on the viscosity of HEC are given in Figs. 3 and 4. The method of least squares was used to obtain the slopes and intrinsic viscosities which are given in Table II. The slopes were approximately proportional to the square of their respective intrinsic viscosities, conforming to the equation derived by Huggins (13):

$$\eta_{\text{sp}/c} = [\eta]_{c=0} + K'[\eta]_{c=0} C \quad \text{(Eq. 2)}$$

where $\eta_{\text{sp}/c}$ = reduced specific viscosity,
$[\eta]_{c=0}$ = intrinsic viscosity,
C = concentration (gramarity),
K' = constant for a homologous series of polymers in a given solvent.

The mean K' value for 35 reduced specific viscosities for HEC-250G was found to equal 1.236 ± 0.430. For the 35 reduced specific viscosities of HEC-250H, the mean K' value was found to equal 1.241 ± 0.458. The fair agreement between mean K' values indicated the validity of the viscosity data obtained. The over-all constant for HEC in water is 1.238 ± 0.444.

Pseudoplastic rheograms for thermally degraded HEC-250G and HEC-250H as a function of time are shown in Figs. 5 and 6, respectively. In each case, the pseudoplasticity of the material diminished with a trend toward Newtonian flow. There was no change in the rheograms of the samples stored at room temperature over the 300-hr. storage.

Molecular Weight–Intrinsic Viscosity Correlation.—The number-average molecular weights determined by osmotic pressure analysis for HEC-250G and HEC-250H were 4.73×10^4 and 1.325×10^5, respectively. The intrinsic viscosities of HEC were related to the corresponding number-average molecular weights by the Kuhn-Houwink (14) empirical equation. Thus,

$$[\eta]_{c=0} = K M^a \quad \text{(Eq. 3)}$$

where $[\eta]_{c=0}$ = intrinsic viscosity,
M = molecular weight,
K and a = polymer–solvent interaction constants.

The constants K and a, valid only for linear polymers, were found to equal 1.445×10^{-4} and 0.9338, respectively. For HEC, therefore, the Kuhn-Houwink equation becomes:

$$\log[\eta]_{c=0} = 0.9338 \, (\log M\bar{n}) + \log 1.445 \times 10^{-4} \quad \text{(Eq. 4)}$$
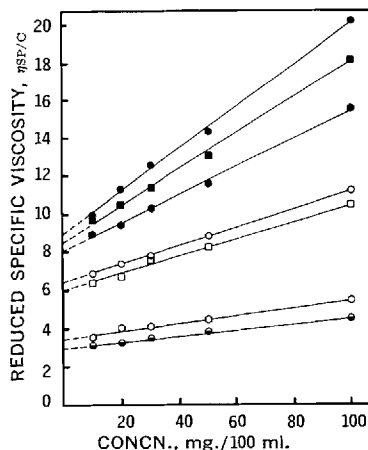

Fig. 4.—Reduced specific viscosity of HEC-250H solutions (1% w/v) thermally degraded at 70°. Key: ●, initial; ■, 24 hr.; closed hexagon, 48 hr.; ○, 96 hr.; □, 147.5 hr.; ◇, 233 hr.; ◐, 306 hr.

TABLE II.—VISCOSITY DATA OF HEC SOLUTIONS TREATED AT 70°

hr., 70°	HEC-250G, 2.0% $[\eta]_c = 0$	Slope	hr., 70°	HEC-250H, 1.0% $[\eta]_c = 0$	Slope
0	3.35	11.2	0	8.85	112.7
24	2.90	10.0	24	8.56	94.9
48	2.55	9.1	48	8.07	74.7
94.5	2.30	4.3	96	6.36	47.7
144	2.05	3.3	147.5	6.02	44.0
192	1.75	3.4	233	3.65	19.0
300	1.40	4.0	306	3.25	12.7

The validity of the interaction constants was tested by determining the intrinsic viscosity of an HEC-250G solution maintained at 70° for 48 hr. The molecular weight, calculated using Eq. 4, was 4.15×10^4; the observed molecular weight from osmotic pressure analysis was 4.199×10^4. The interaction constants, K and a, for HEC in water were, therefore, assumed to be valid.
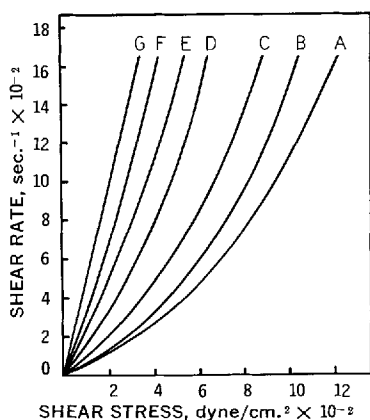

Fig. 5.—Pseudoplastic rheograms of 2% w/v HEC-250G solutions thermally degraded at 70°. Key: A, initial; B, 24 hr.; C, 48 hr.; D, 94.5 hr.; E, 144 hr.; F, 192 hr.; G, 300 hr.
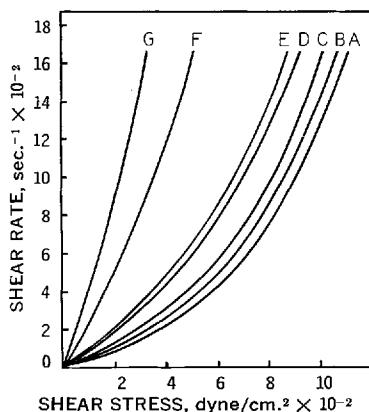

Fig. 6.—Pseudoplastic rheograms of 1% w/v HEC-250H solutions thermally degraded at 70°. Key: A, initial; B, 24 hr.; C, 48 hr.; D, 96 hr.; E, 147.5 hr.; F, 233 hr.; G, 306 hr.

Degradation Rate and Viscosity Half-Life.—The thermal viscosity degradation of HEC in water was found to best approximate a first-order reaction rate (Fig. 7). Viscosity degradation parameters are given in Table III along with the linear correlation coefficients.

The reaction rate constant for the degradation of HEC-250H is approximately 1.5 times greater than that of HEC-250G. This would indicate that the higher molecular weight 250H is more prone to thermal degradation than 250G, even though the concentration of HEC-250H was half that of HEC-250G and the initial pseudoplastic rheograms were nearly identical (Figs. 5 and 6).

DISCUSSION

The mechanical degradation study indicates that the two molecular weight grades of HEC are capable of withstanding intensive hydrodynamic shear rates. Only under the most rigorous conditions where a shear rate of 1.88×10^6 sec.$^{-1}$ was maintained for 90 min. was HEC-250H (1.0%) found to degrade. Analysis showed that a 15% reduction in molecular weight and intrinsic viscosity had been affected. These findings are in accordance with other investigations (2, 3), where it was noted that mechanical shear had little effect on polymers, in this case noncellulosics, of molecular weights less than 5×10^5.
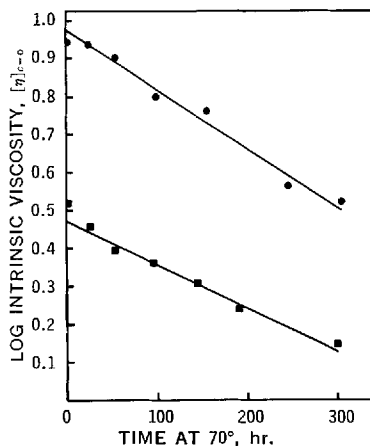

Fig. 7.—Degradation rate curves of aqueous HEC solutions at 70°. Key: ●, HEC-250H (1% w/v); ■, HEC-250G (2% w/v).

TABLE III.—VISCOSITY DEGRADATION DATA FOR HEC SOLUTIONS TREATED AT 70°

Mol. Wt. Grade	Reaction Rate Constant, hr.$^{-1}$	Slope	Viscosity Half-Life, hr.	Linear Correlation Coefficient
HEC-250G	2.58×10^{-3}	-1.12×10^{-3}	268.5	0.992
HEC-250H	3.64×10^{-3}	-1.58×10^{-3}	190.8	0.974

The mechanism associated with the thermal degradation and subsequent reduction in viscosity and molecular weight of HEC solutions is believed to be random hydrolysis of the glycosidal linkages. This proposed mechanism is in accordance with other degradation studies (6, 9, 10) involving cellulose derivatives. Hydrolytic cleavage of hydroxyethyl side chains or pyranose rings may also occur but is not likely to cause the marked viscosity changes found in this study. The extensive release of hydroxyethyl units would decrease the polymer solubility by conversion to cellulose; however, no turbidity was noted in the degraded samples. Rupture of the pyranose rings would not effectively alter chain length or molecular weight.

The relative viscosity stability and degradation rates of the two molecular weight grades of HEC at 70° indicates that when viscosity control is necessary, it is advantageous to employ a higher concentration of lower molecular weight polymer. It was shown that the pseudoplasticity of a 2% HEC-250G solution was nearly identical to that of a 1% HEC-250H solution, but that the viscosity half-life of the lower molecular weight 250G was 1.5 times greater than the 250H.

SUMMARY

A study was undertaken to determine the viscosity stability of two molecular weight grades of HEC. Polymers in aqueous solutions were subjected to processing conditions allied with the manufacture of pharmaceutical dispersed systems.

The intrinsic viscosity, pseudoplasticity, and molecular weight of two grades of HEC were not affected by the more moderate shearing operations used. In one case, under extremely rigorous shearing conditions, the higher molecular weight grade (HEC-250H) showed a significant viscosity and molecular weight reduction.

It was hypothesized that the decrease in viscosity at 70° was due to hydrolysis of glycosidal linkages; this was supported by number-average molecular weight analysis.

Good correlation between intrinsic viscosity and number-average molecular weight enabled calculation of the interaction constants in the Kuhn-Houwink equation. The constant of the Huggins equation relating dilute viscometry slope to the square of intrinsic viscosity was also calculated.

Thermally induced degradation of HEC was found to approximate a first-order rate law with high linear correlation.

The viscosity degradation rate for 1% HEC-250H was approximately 1.5 times that of 2% HEC-250G. This indicated that the higher molecular weight grade was more prone to thermal degradation than the lower molecular weight grade.

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