

Assay of Hydroxypropoxy Group in Hydroxypropyl Cellulose by United States Pharmacopeia-Titration Method

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Abstract Hydroxypropyl cellulose (HPC) is a derivative of cellulose with both water soluble and organic solubility, used as food additive and sieving matrix for DNA separation. Hydroxypropyl Cellulose is partially substituted poly (hydroxypropyl) ether of cellulose. It contains NLT 53.4% and NMT 80.5% of hydroxypropoxy groups, calculated on the dried basis. It may contain ether suitable anticaking agents, and 0.6 percent of silica (SiO₂). The average sample result has been determined 67.3% which was conforms to USP/NF specifications for Hydroxypropyl cellulose.

Keywords: Hydroxypropoxy group, Hydroxypropyl Cellulose, assay test

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1. Introduction

Hydroxypropyl cellulose (Cellulose, 2-hydroxypropyl ether) (HPC) is an ether of cellulose where some of the hydroxyl groups of the cellulose have been hydroxypropylated forming -OCH₂CH(OH)CH₃ groups using propylene oxide. Chemical formula of Hydroxypropyl ether of cellulose is [C₆H₇O₂(OH)_x(OCH₂CHOHCH₃)_y(OCH₂CH[R_w]CH₃)₂]_n. R is a substituent comprising "w" hydroxypropoxyl group. Structural formula is shown at Figure 1. HPC is a nonionic water soluble cellulose ether with a remarkable combination of properties. It combines organic solvent solubility, and surface activity. HPC is a white or yellowish-white powder or granules, hygroscopic after drying soluble in cold water in glacial acetic acid, in anhydrous ethanol, in methanol and in propylene glycol and in a mixture of 10 parts of methanol and 90 parts of methylene chloride giving colloidal solutions, sparingly soluble or slightly soluble in acetone, practically insoluble in hot water, in ethylene glycol and in toluene. [1]

HPC is used as a lubricant for severe dry eye syndromes. [2,3,4] HPC is also used as a thickener, a low level binder and as an emulsion stabilizer with E number E₄₆₃. In pharmaceuticals it is used as a binder [5] in tablets. HPC is also used as a food additive, sieving matrix for DNA separations by capillary and microchip electrophoresis [6].

Hydroxypropyl cellulose is a physiologically inert substance, in a study of rats fed hydroxypropyl cellulose or unmodified cellulose at levels up to 5% of their diet; it was found that the two were biologically equivalent in that neither was metabolized. HPC is not absorbed from the

gastrointestinal tract and is quantitatively excreted in the faces.

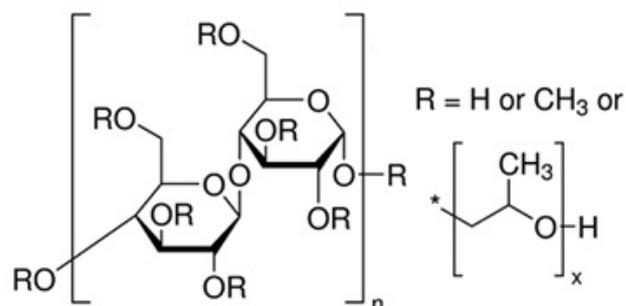


Figure 1. Structural formula of Hydroxypropyl Cellulose

2. Materials and Method

2.1. Apparatus and Chemicals

2.2.1. Reagents

- Sodium bicarbonate, NaHCO₃
- Potassium iodide. KI
- Hydroxypropylcellulose raw materials were supplied by DOW USA Chemical Corporation, F4M premium grade

2.2.2. Solutions

- D. I Water
- Chromium Trioxide Solution
- 0.02N Sodium Hydroxide Volumetric Solution

- Sodium bicarbonate
- 2N Sulfuric acid Test Solution
- Potassium Iodide
- 0.02N Sodium Thiosulfate Volumetric Solution
- Starch Indicator test solution.
- USP Hydroxypropyl Cellulose RS

2.3. Equipment

- Analytical balance
- Thermometer
- Timer
- Hydroxypropoxy determination apparatus (reaction flask).

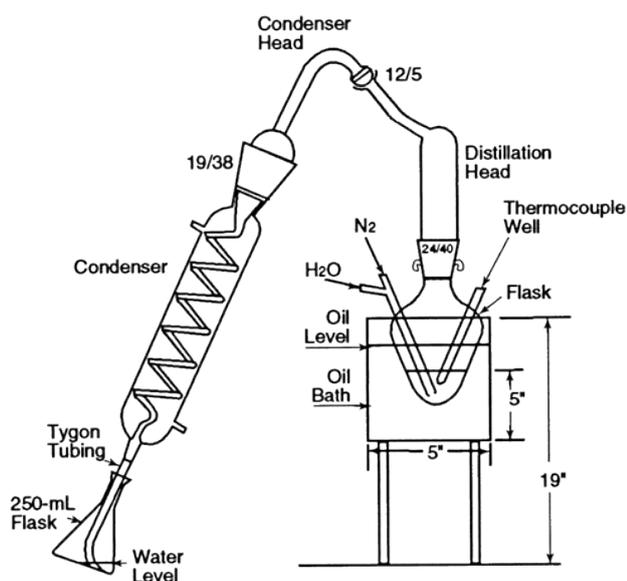


Figure 2. Reaction flask for hydroxypropoxy determination [1]

The boiling or reaction flask, consisting of a 125-mL conical-bottom boiling flask modified to provide a thermocouple (or thermometer) well and an inlet with a 1.0-mm capillary tip for nitrogen and water is fitted with a distillation head that leads to a condenser. The reaction flask is immersed in an oil bath equipped with an electric heater capable of heating the bath at the desired rate and maintaining the temperature at 155°. The distillate is collected in a flask. [NOTE—the tube from the condenser to the flask must be below the surface of the liquid in the flask to ensure the capture of all of the acetic acid formed [Figure 2] [1].

3. Procedure Analysis

Transfer about 65 mg of Hydroxypropyl Cellulose, previously dried at 105° for 1 hour and accurately weighed, into the reaction flask. Add 5 mL of water, and swirl gently for 5 minutes. Add 10 mL of chromium trioxide solution (30 g in 70 mL). Assemble the apparatus as shown in Figure 2 and immerse the reaction flask in the oil bath slightly above the level of the chromium trioxide solution. Start the condenser cooling water, and pass nitrogen gas through the flask at a rate of about 70 to 75

mL per minute. Raise the temperature of the oil bath to 155° during a 30-minute period, and maintain it at this temperature throughout the determination. [NOTE—too rapid an initial rise in temperature results in high blank determinations. Monitor the temperature of the reaction mixture in the reaction flask using a thermocouple or thermometer in a well, as shown in Figure 2. When a reaction mixture temperature of $102 \pm 1^\circ$ is reached, add water through the water inlet until the reaction mixture temperature drops to $97 \pm 1^\circ$. Continue this 97° to 102° temperature cycle until 100 mL of distillate has been collected. Detach the condenser from the distillation head, and wash with water, collecting the washings in the flask containing the distillate. Titrate the solution with 0.02 N sodium hydroxide VS to a pH of 7.0 ± 0.1 , using an expanded-scale pH meter equipped with glass and calomel electrodes. Record the volume, V , of the 0.02 N sodium hydroxide used, then add 500 mg of sodium bicarbonate and 10 mL of 2 N sulfuric acid. After evolution of carbon dioxide has ceased, add 1 g of potassium iodide, insert the stopper in the flask, shake the mixture, and allow the solution to stand in the dark for 5 minutes. Titrate the liberated iodine with 0.02 N sodium thiosulfate VS to the sharp disappearance of the yellow iodine color, adding a few drops of starch TS to confirm the endpoint. Record the volume, Y , required. This titration, Y mL, multiplied by the empirical factor, K , appropriate to the particular apparatus and reagents in use (see calculation below), gives the acid equivalent not caused by acetic acid. The acetic acid equivalent is $(V = KY)$ mL of 0.02N sodium hydroxide.

Obtain the empirical factor, K , for the apparatus by performing a blank determination in which the Hydroxypropyl Cellulose is omitted. The acidity of the blank for a given apparatus and given reagents is in a fixed ratio to the oxidizing equivalent of the distillate in terms of sodium thiosulfate:

$$K \text{ factor} = (V_B \times N_1) / (Y_B \times N_2)$$

in which V_B is the volume, in mL, of 0.02 N sodium hydroxide required in blank run; N_1 is the normality of the 0.02 N sodium hydroxide; Y_B is the volume, in mL, of 0.02 N sodium thiosulfate required in blank run; and N_2 is equal to the normality of the 0.02 N sodium thiosulfate.

Calculate the percentage of hydroxypropoxy groups ($-\text{OCH}_2\text{CHOHCH}_3$) by the formula:

$$100(V_A N_1 - K Y_A N_2)(0.079 / W)$$

in which V_A is the volume, in mL, of 0.02 N sodium hydroxide required for titration of the sample; N_1 is the normality of the 0.02 N sodium hydroxide; K is the empirical factor; Y_A is the volume, in mL, of 0.02 N sodium thiosulfate required for titration of the sample; N_2 is the normality of the 0.02 N sodium thiosulfate; and W is the quantity, in g, of sample used. Each mL of 0.02 N sodium hydroxide is equivalent to 1.502 mg of hydroxypropoxy groups ($-\text{OCH}_2\text{CHOHCH}_3$) [7].

The results obtained as a percentage of hydroxypropoxy content may be converted to terms of average molecular substitution of glucose units by means of the accompanying graph (Figure 3)

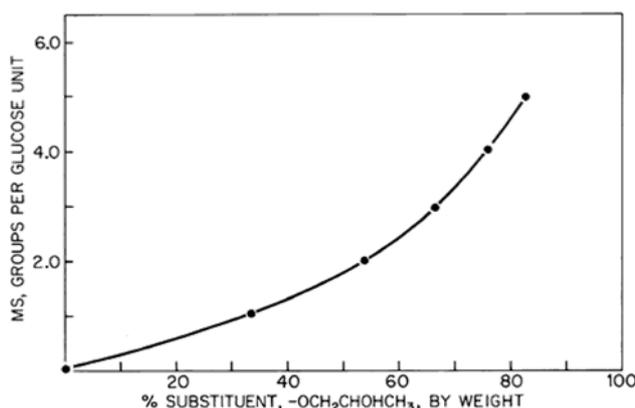


Figure 3. Graph for converting percentage of substitution, by weight, of hydroxypropoxy groups to molecular substitution per glucose unit [1]

4. Result and Discussion

4.1. Calculations for Hydroxypropylcellulose

65.0 mg of hydroxypropylcellulose was swirled in 5 mL water for 5 min. To this was added 10 mL of 30g/70 mL Cr₂O₃ solution to optimize dissolution of sample. Take ½ hr to reach operating temperature, with argon flowing, on oil bath, as per official monograph.

Titrated with 0.01947 N NaOH (as standardized with HCl) to pH 7.00. Sample was required 28.90 mL of NaOH. A blank was required 0.20 mL of NaOH. Then add 0.5 g NaHCO₃ and 10 mL of 2N H₂SO₄; after production of

CO₂ (g) ceases, add 1 g KI, stopper and shake, kept in dark for 5 min, and titrated with 0.020M thiosulfate. Sample was required 0.80 mL thiosulfate; blank was required 0.02 mL thiosulfate (Table 1).

$$K = \frac{(VB \times N1)}{(YB \times N1)} = \frac{0.20 \times 0.01947}{0.30 \times 0.02030} = 0.6394$$

% Hydroxypropoxy groups

$$= (V_A N_1 - K Y_A N_2) \times \left(\frac{0.079}{W} \right) \times 100$$

Test A

% Hydroxypropoxy groups

$$= (28.90 \times 0.01974 - 0.6394 \times 0.80 \times 0.02030)$$

$$\times \left(\frac{0.079}{0.0658} \right) \times 100$$

$$= 67.25\%$$

Test B (duplicate)

% Hydroxypropoxy groups

$$= (28.88 \times 0.01974 - 0.6394 \times 0.78 \times 0.02030)$$

$$\times \left(\frac{0.079}{0.0656} \right) \times 100$$

$$= 67.44\%$$

Average of percent Hydroxypropoxy groups: 67.3%, and meets the United States Pharmacopeia (USP/NF) specification for Hydroxypropyl cellulose.

Table 1. Results for Assay

| Identity | Volume V _A of the 0.02 N NaOH (mL) | Volume Y _A , Y _B of the 0.02 N Na ₂ S ₂ O ₃ (mL) | Empirical factor, K $\frac{(VB \times N1)}{(YB \times N2)}$ | Sample weight (mg) | Normality of NaOH | Normality of S ₂ O ₃ | Hydroxypropoxy Groups (%) |
|----------|---|---|---|--------------------|-------------------|--|---------------------------|
| Blank | 0.20 | 0.02 | 0.6394 | ----- | 0.01947 | 0.02030 | ----- |
| Test A | 28.90 | 0.80 | ----- | 0.0658 | 0.01947 | 0.02030 | 67.25 |
| Test B | 28.88 | 0.78 | ----- | 0.0656 | 0.01947 | 0.02030 | 67.44 |

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