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De-acetylated PVA for Pharmaceutical Hydrogel Applications

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Commercially available grades of fully hydrolyzed PVA are not 100% hydrolyzed. In practice, these polymers actually have residual acetyl groups. The remaining unhydrolyzed PVA can be hydrolyzed to 100%, but the subsequent purification process has proven to be difficult. A new method has been proposed to improve the purification process by using a freeze-thaw method. The final products after purification have been analyzed by using FTIR and ^{1}H-NMR spectroscopic methods.

Keywords: PVA, fully hydrolyzed, de-acetylated, hydrogel

1 Introduction

Poly(vinyl alcohol) (PVA), as an excellent water-soluble polymer, has a wide range of industrial applications (1). It can be prepared by hydrolysis of poly(vinylacetate) (PVAc). (2,3). PVA and its derivatives acquire special attention in the areas of drug delivery, adhesives, membranes, paper, and many other applications (4–8). The final physical and chemical properties of PVA depend on the synthetic conditions and degree of hydrolysis of the polymer.

Fully hydrolyzed PVA is a commercially available product. The term "fully hydrolyzed PVA" is generally recognized in the trade as highly hydrolyzed polyvinyl ester (i.e., 99+ % hydrolyzed PVA). These polymers have residual acetyl groups remaining in the polymer. In many applications, this small amount of acetyl groups does not impair its usefulness. But in some cases, the residual acetyl groups may react chemically to generate unwanted side reactions during formulation. For example, PVA is used in our lab for making pharmaceutical hydrogels that serve as drug reservoirs in electrotransport drug delivery systems (9). In this specialized application, the residual acetyl groups undergo hydrolysis which leads to unwanted shifts in pH during the operation of the delivery system (10). The exact mechanism for this shift is currently under investigation. Human skin has an isoelectric point of about pH 4 (11). A formulation pH above 4 will result in increased transport of drug (cation), and pH below 4 will result in increased transport of anions. Therefore, a pH of 4 or above is targeted for our PVA formulation. In this work, we have explored pretreating the PVA by de-acetylating the polymer prior to it being used as a hydrogel polymer in electrotransport applications. IR and NMR spectroscopic methods were used to characterize the final products.

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2 Experimental

2.1 Materials

PVA (Mowiol 10-98) was purchased from Fluka. The degree of polymerization and hydrolysis were 1400 and 98.0-98.8%, respectively. NaOH pellets and DMSO-*d*6 (99.96 atom % D) were purchased from Aldrich. Ultra pure de-ionized water was used as solvent in all experiments. All chemicals were used without further purification.

2.2 PVA Hydrolysis Reaction

PVA (3.75 g, 85.2 mmol) was added to a reaction flask with a stir bar. 10 mL of various calculated concentration of NaOH solution was then added to the flask. The reaction mixture was allowed to stir for 12 h at room temperature. The liquid fraction was decanted and discarded. A 5 mL portion of ultra pure de-ionized water was then added back to solids to start a water extraction process. The product mixture was allowed to stir for a given amount of time (approximately 20 h) before liquid was decanted, filtered under pressure with a syringe through a 0.8 micron filter, and collected. This procedure was repeated for 25 cycles.

The resulting filtrates were then analyzed for sodium and acetate contents.

2.3 Sodium Concentration Determination

Sodium contents were determined by using a Dionex ICS2000 ion chromatography system. This system was equipped with MSA cartridge, CS-RS suppressor (4 mm), and CR-CTC cation trap column. The column used was Dionex IonPac CS12A (4 × 250 mm) and the mobile phase was 28 mM MSA. Serial dilution of Dionex Six Cation-II Standard was used to prepare eight standard solutions from 0.4 to 101.5 μg/mL. The signal response from these standards was used to plot a working curve. All samples for analysis were diluted to appropriate concentration before measurement.

2.4 Acetate Concentration Determination

Acetate contents were determined by using a Dionex DX500 system. This system was equipped with KOH cartridge, ASRS suppressor (4 mm), and CR-TC anion trap column. The column used was Dionex IonPac AS18 (4 × 250 mm) and the mobile phase was 23 mM KOH. Eight working standards were prepared by serial dilution of the Fluka 1000 ppm acetate standard ranging from 0.1 to 100 μg/mL acetate. All samples for analysis were diluted to appropriate concentration before measurement.

2.5 FTIR Measurements

FTIR spectra of the hydrolyzed PVA products were measured on a Thermo Electron Corporation Nicolet 6700 Fourier Transform Infrared (FTIR) spectrometer. Thin films were made from the final products prior to analysis. For all samples, 0.03 g of polymer was dissolved in 1 g of di-H_2O at 80°C. The resulting solution was evenly distributed into 3 molds (3.33 mL in 0.5 in. dia × 0.0625 in. deep) in a Teflon sample plate via a pipet. The samples were dried at room temperature for 48 hours to form thin films. The thin films were then carefully peeled from the Teflon sample plate and further dried in an 90°C oven for 48 h to remove possible water trapped in the polymer.

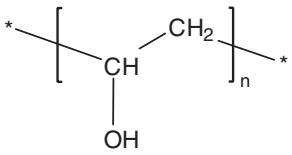
2.6 NMR Measurements

^{1}H-NMR spectra were recorded on a JEOL (Japan Electric Co., Ltd.) Eclipse$^+$ 400 MHz FT-NMR spectrometer at 70°C. Samples were pre-dissolved in an 70°C oil bath with deuterated water before transferred to 5-mm NMR tubes. A sample concentration was approximately 10 mg per mL of deuterated solvent. Tetramethylsilane (TMS) was added as the internal standard.

3 Results and Discussion

3.1 IR and ^{1}H NMR Characterization of Stock PVA

Commercially available fully hydrolyzed PVA (**1**) always has a small amount (i.e. < 1%) of unhydrolyzed vinyl acetate (VAc). The carbonyl band from VAc can be easily detected by FTIR. As shown in Figure 1, the carbonyl bands for fully hydrolyzed PVA purchased from Fluka are at 1708 and 1735 cm^{-1}. The band at 1708 cm^{-1} is from hydroxyl associated carbonyl signal, and the band at 1735 cm^{-1}, appears as the shoulder of 1708 cm^{-1}, is from free carbonyl of acetate ion (12). Other major characteristics of PVA included are a broad hydroxyl band at 3329 cm^{-1} and a C-O stretching vibration at 1090 cm^{-1}.



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^{1}H-NMR has also been used to detect VAc in commercially available fully hydrolyzed PVA. As shown in Figure 2, the methyl group from VAc is located at 2.11 ppm in D_2O. The groups of signals centered at 1.7 ppm are the methylene protons from PVA. The integration of the methyl group at 2.1 ppm comes out to be 2.8 when an integration value of 200 is used for the methylene signals. That means approximately one percent of unhydrolyzed PVA is present in the commercially available fully hydrolyzed PVA. Other signals in the ^{1}H-NMR spectrum are the methane and the hydroxyl signals of PVA. The methane signal shows up as a broad peak centered at 4.03 ppm. The hydroxyl groups are exchanging with D_2O and they appear as a sharp signal at 4.33 ppm.

3.2 Hydrolysis Reaction

Hydrolysis of PVA (3.75 g) was carried out with three different concentrations of NaOH solution. 10 grams of 100 mM, 300 mM, and 500 mM NaOH had been used for the reactions. They correspond to 0.012, 0.035, and 0.059 equivalent of PVA, respectively. The NaOH concentration was kept low because excess NaOH was difficult to remove after the hydrolysis reaction. It was important to rinse out all excess NaOH from PVA at the end of the reaction. Any unwanted cations or anions remaining in a PVA-based hydrogel could be the source of a problem as they compete with the charged drug during electrotransport.

A total of 24 extractions were carried out after the hydrolysis reactions. All sample filtrates from the 24 extractions were analyzed for sodium and acetate contents. The results are shown in Figure 3. As expected, excess sodium and acetate can be extracted by water. More extractions were

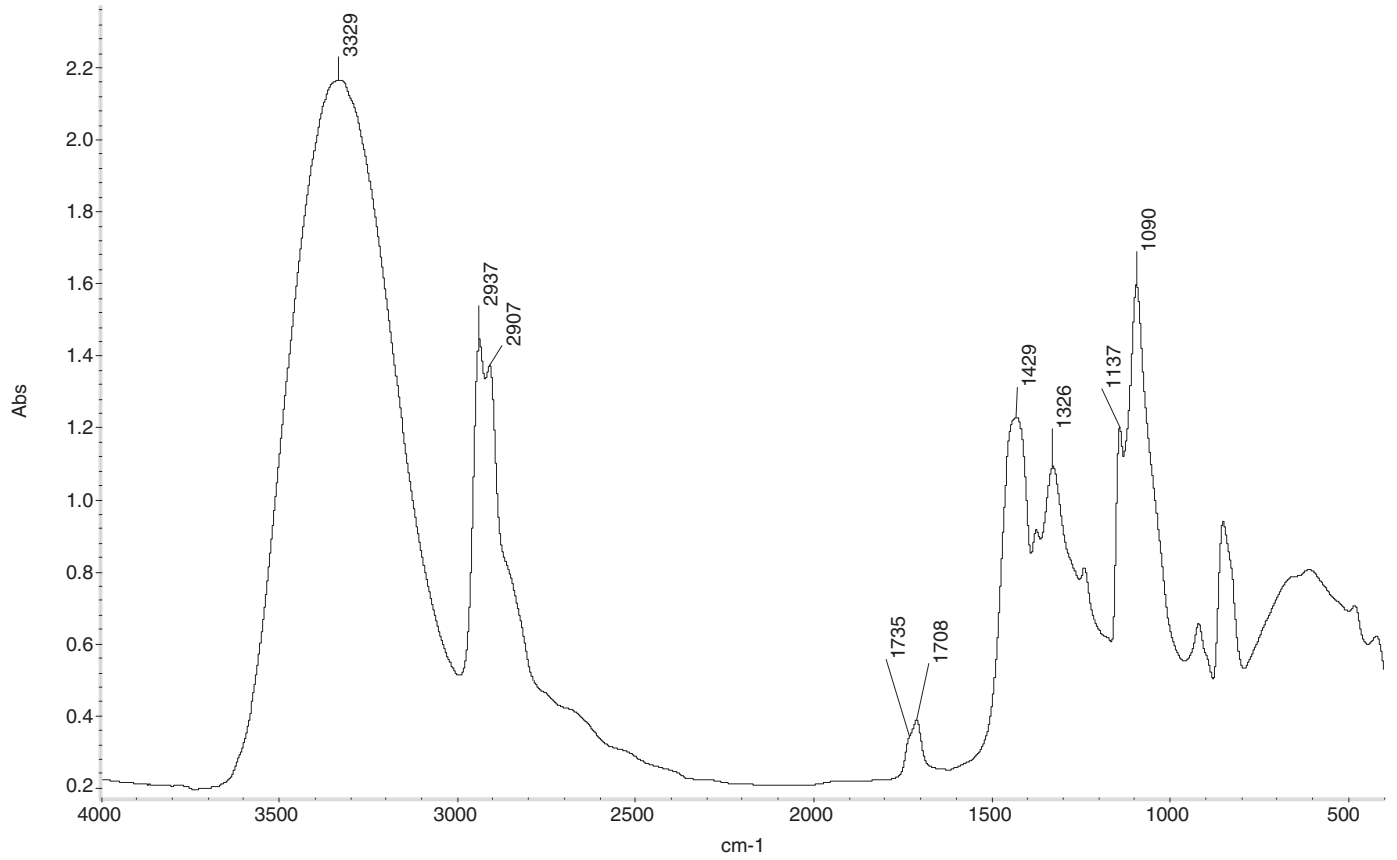

Fig. 1. Infrared spectrum of stock fully hydrolyzed PVA (Fluka, Mowiol 10-98).

needed when a higher initial concentration of NaOH was used. As many as 15 days and 23 extractions were required for the sodium and acetate level to reach equilibrium at 3 ppm for the 500 mM NaOH used. 10 days and 18 extractions were needed for the 300 mM reaction. 6 days and 12 extractions were needed for the 100 mM reaction.

The pH of all sample filtrates was also monitored. As shown in Figure 4, the pH of all three sets of filtrate samples level out at approximately 7.4. The results are similar to sodium and acetate analysis (Fig. 3). More extractions are needed when higher concentration of NaOH used. Typically, approximately 12 extractions for a 100 mM reaction, 18 extractions for a 300 mM reaction, and 23 extractions are needed for a 500 mM reaction. Therefore, we can assume that the pH is in direct relationship with sodium and acetate contents. The concentrations of sodium and acetate are at approximately 3 ppm when the pH of the sample reached its equilibrium.

All three hydrolyzed PVA samples were checked for pH stability in an electrotransport drug delivery system. The hydrogel formulation prepared from 100 mM NaOH treated PVA still had an observable pH decrease during electrotransport operation. By contrast, no pH decreases were observed for the formulations prepared from 300 mM and 500 mM NaOH treated PVA. Therefore, hydrolysis of PVA was optimal with 300 mM NaOH solution. Treatment with this concentration provides a sufficient extent of de-acetylation and the hydrolysis byproducts extract more readily than the 500 mM treatment.

3.3 Simplified Purification Procedure

Residual sodium and acetate are clearly difficult to remove from PVA after a NaOH hydrolysis reaction. It has taken 10 days and 18 extractions for the sodium and acetate concentration to reach their equilibrium for the 300 mM reaction. A continuous washing procedure has been set up for this purpose. PVA was treated overnight with calculated volume of 300 mM NaOH solution in an addition funnel. The NaOH solution was allowed to drain completely. A hose was then connected from an ultra-pure deionized water source to the top of the addition funnel. Deionized water was pumped into the additional funnel with a controlled rate. Water was rinsed continuously through the PVA sample and drained from the funnel. pH of the drained water was continuously monitored. Since pH is related to sodium and acetate contents based on previous experiments, it is assumed that a sample with neutral pH has approximately 3 ppm of sodium and acetate contents. Therefore, a neutral pH means the washing cycle is completed. The washing

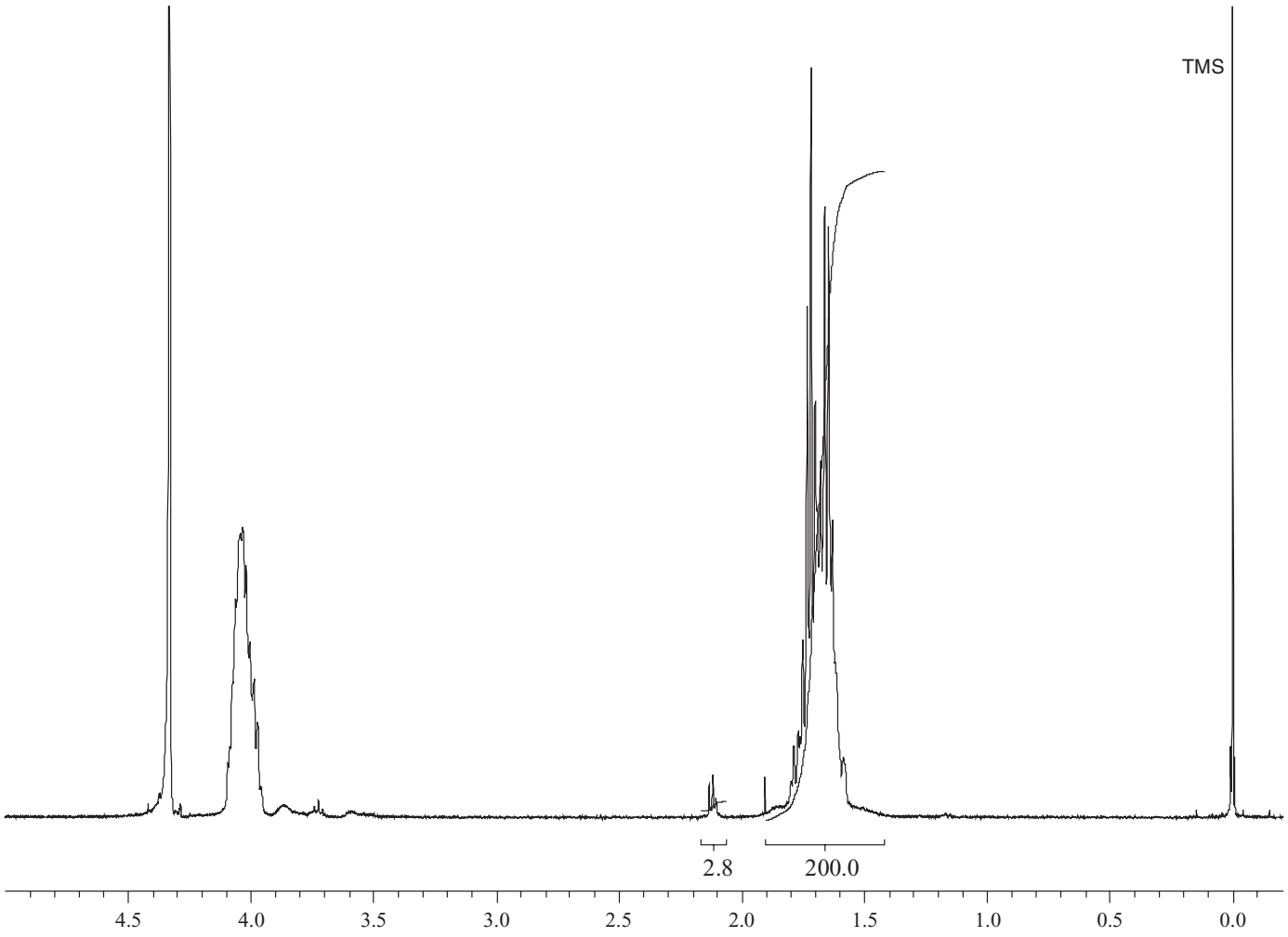

Fig. 2. 400 MHz ^{1}H-NMR spectrum of stock fully hydrolyzed PVA (Fluka, Mowiol 10–98) dissolved in D_2O at 70°C.

process took 72 h. This is still a long duration of time and a procedure with shorter washing cycle could be useful.

PVA in solid state is well packed and highly crystalline (13,14). Sodium and acetate trapped within the polymer after hydrolysis are proven difficult to remove. If the crystallinity of PVA is disrupted, ions trapped within the polymer might elute out more readily. A reaction was done based on this hypothesis. Stock PVA was dissolved in 80°C di-water and calculated amount of NaOH was added to the solution. The polymer solution was allowed to cool down

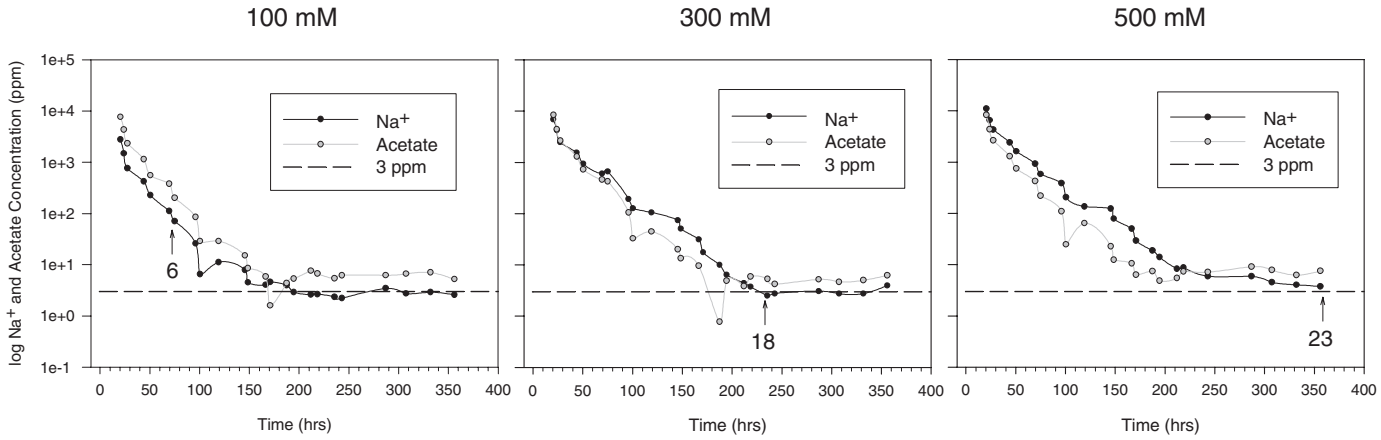

Fig. 3. Sodium and acetate profiles of aqueous extractions of PVA after hydrolysis.

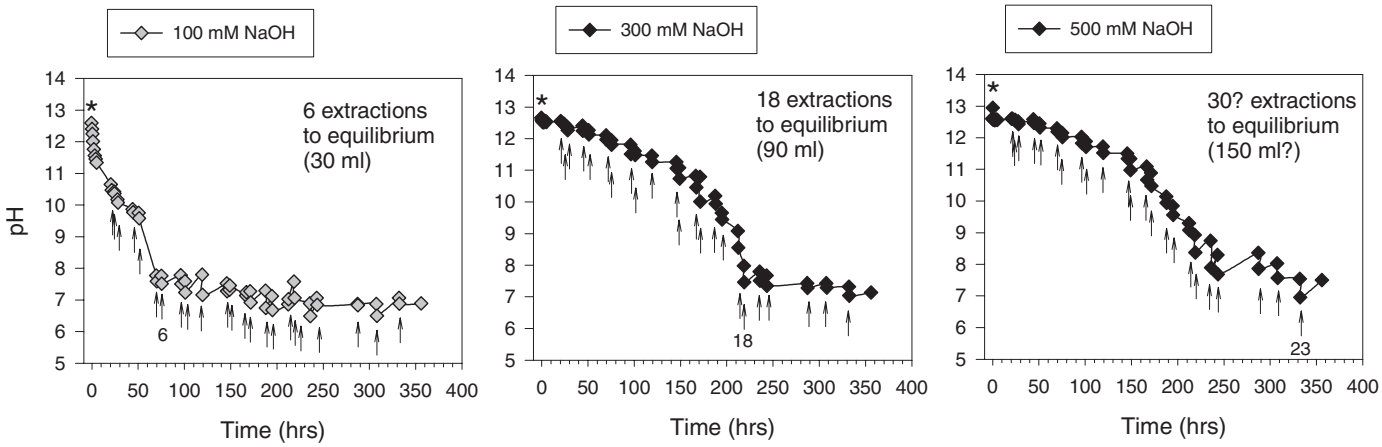

Fig. 4. pH profiles of aqueous extraction of PVA after hydrolysis.

to room temperature. A single-cycle freeze-thaw procedure was then applied to physically cross-link the polymer (15). The physically cross-linked PVA polymer was cut into small pieces and transferred into an addition funnel. Ions trapped in the PVA hydrogel system are much easier remove when compared to ion trapped in highly crystalline PVA in solid state. A continuous washing procedure was applied as described previously. The washing time of the gel has been significantly lowered to 12 h from 72 h for the pH to reach equilibrium at 7.4. Therefore, this procedure is much more effective method to purify PVA after hydrolysis reactions.

3.4 IR and ^{1}H-NMR Characterization of Fully Hydrolyzed PVA

Fully hydrolyzed PVA products after hydrolysis and purification had been analyzed by FTIR and ^{1}H-NMR spectroscopic method. Figure 5 is a FTIR spectrum of

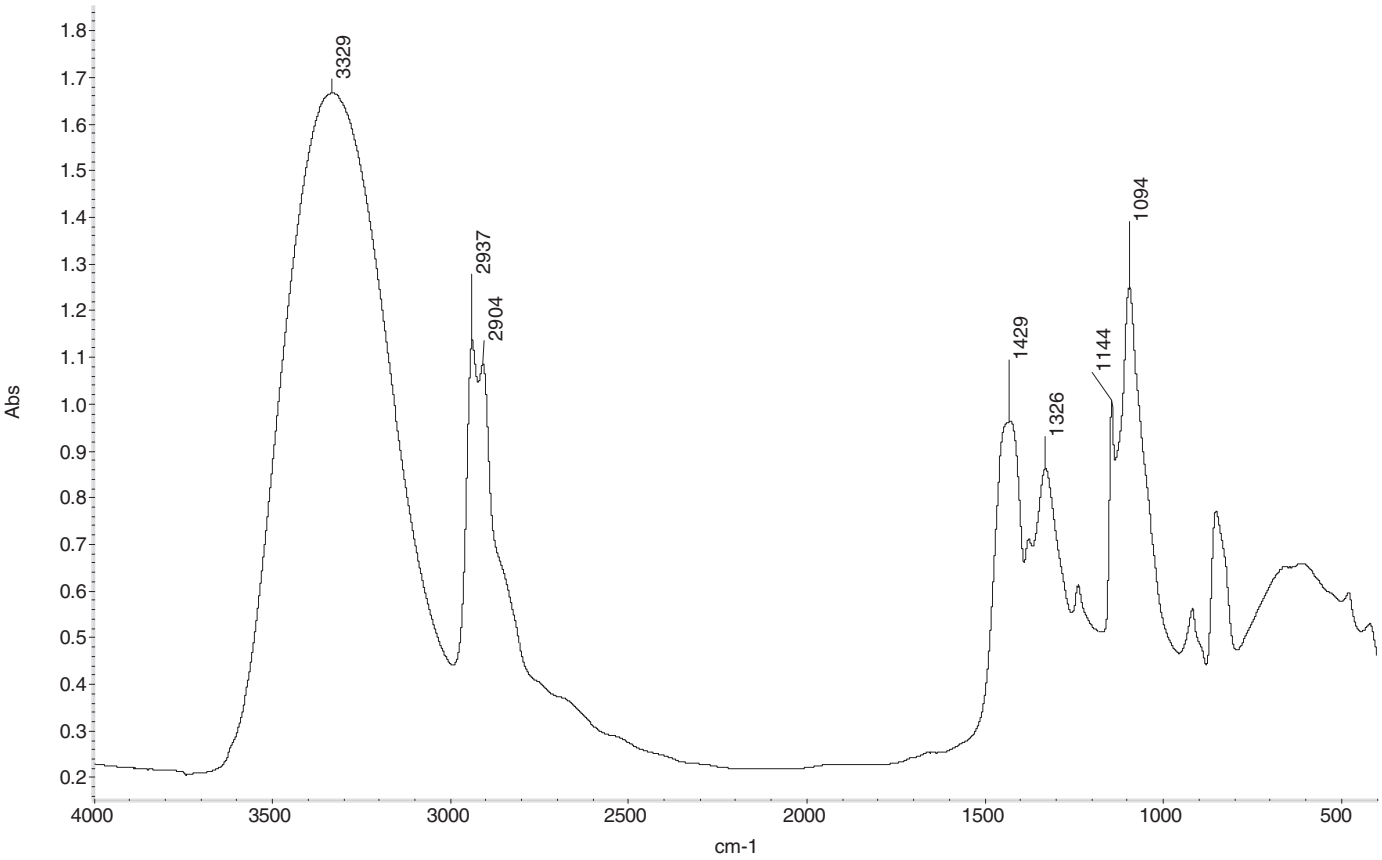

Fig. 5. Infrared spectrum of PVA after hydrolysis and purification.

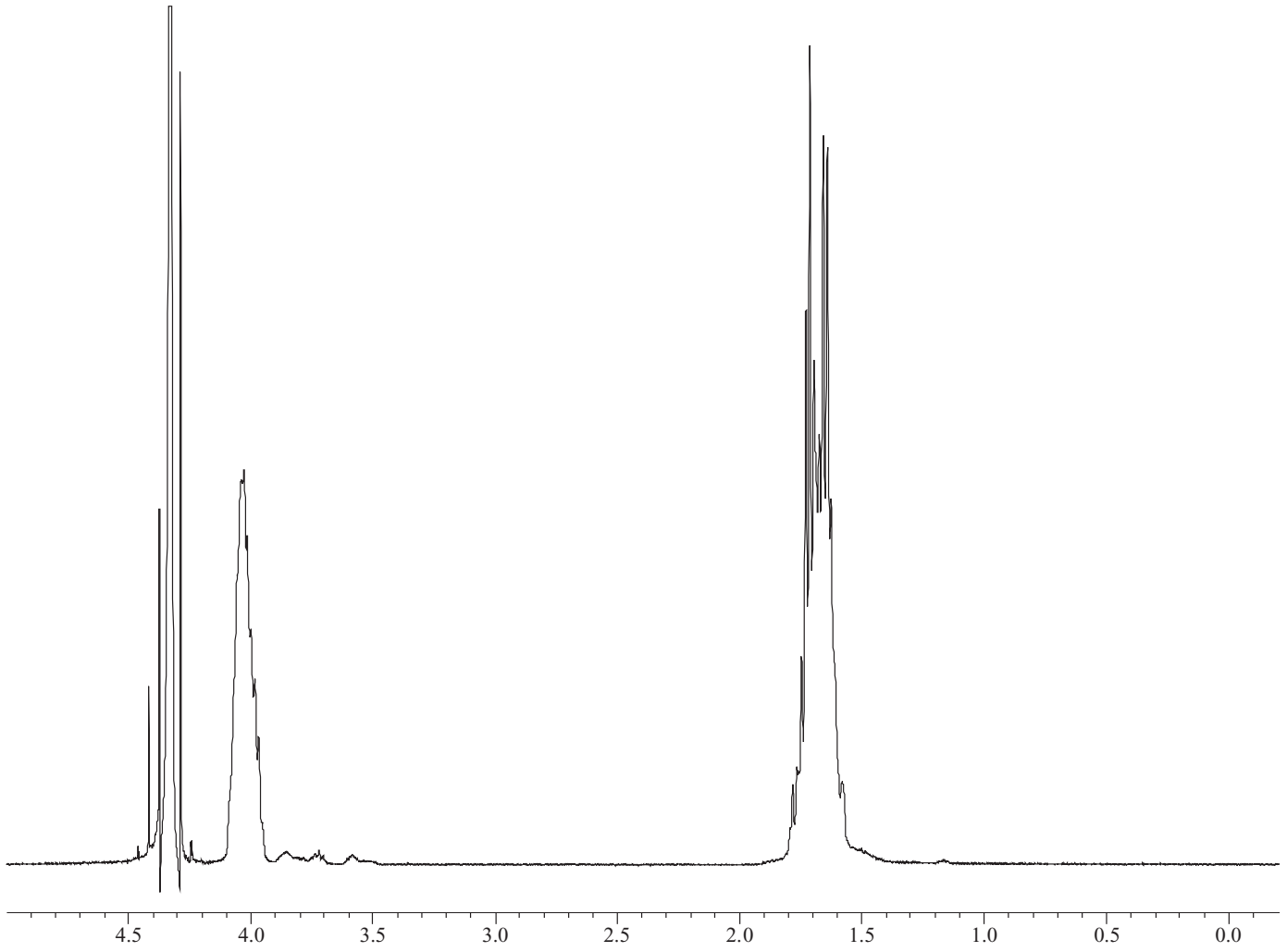

Fig. 6. 400 MHz ^{1}H NMR spectrum of PVA after hydrolysis and purification (D_2O at 70°C).

the final product. The carbonyl signals at 1708 and 1735 cm^{-1} have been completely eliminated when compared to stock PVA shown in Figure 1. FTIR is a technique that is extremely sensitive to carbonyl signals. The absence of carbonyl signal in Figure 5 means all VAc from stock PVA has been replaced with hydroxyl groups via hydrolysis reaction. This also means that the side product, sodium acetate, was completely washed out. Since the concentration of acetate is related to sodium content (Fig. 3), we can assume that sodium content is at its minimum.

^{1}H-NMR has also been used to analyze VAc content from the final products. The signals representing the methyl group on VAc at 2.11 ppm (Fig. 2) are now completely eliminated (Fig. 6). This result is in good agreement with the IR data.

4 Conclusions

Commercially available fully hydrolyzed PVA is not 100% hydrolyzed. It has residual acetyl groups remaining in the polymer. A hydrolysis reaction can further hydrolyze the residual acetyl groups to completion. Purification of PVA has been proven difficult after hydrolysis reaction. A long period of time and a large number of extractions by using water were needed to fully remove the residual ions. A new method has been introduced to improve the purification process. The idea is to disrupt crystallinity of PVA via freeze-thaw method after hydrolysis reaction. Unwanted residual ions can be easily removed by continuous washing with di-water. The time for purification has been shortened to 12 h when compared to approximately 10 days from the original method. IR and NMR spectroscopic methods have been used to analyze the final purified products. The signals representing VAc have been completely eliminated. Fully hydrolyzed PVA is now available for high quality pharmaceutical hydrogel and other applications.

Acknowledgments

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15. A single-cycle freeze-thaw procedure is to freeze PVA solution at -40°C for an hour and then warm up to 5°C for another hour before storage at room temperature.